The Role of Lifestyle Factors and Personality for the Prevention of Cancer and Other Noncommunicable Diseases

---

Dissertation

zur

Erlangung der naturwissenschaftlichen Doktorwürde
(Dr. sc. nat.)

vorgelegt der

Mathematisch-naturwissenschaftlichen Fakultät

der

Universität Zürich

von

Tina Lohse

aus

Deutschland

Promotionskommission

PD Dr. Sabine Rohrmann (Vorsitz)
Prof. Dr. Torsten Hothorn
Prof. Dr. Nicole Probst-Hensch
PD Dr. David Fäh

Zürich, 2017

Danksagung

Ich bedanke mich herzlich bei Dr. Sabine Rohrmann und Dr. David Fäh für die erfolgreiche Betreuung meines Doktorates. Die Arbeit mit Dr. Sabine Rohrmann, Prof. Monika Eichholzer und Dr. Aline Richard war stets mit Freude erfüllt und ich werde auf die Zeit in der ich mit ihnen im Team zusammenarbeiten durfte immer dankbar zurückblicken. Ich möchte mich auch bei Christine Leuthold, Nina Pupikofer, Dr. Rolf Heusser, Dr. Jean-Philippe Krieger, Sophie Cabaset und Fabienne Hartmann sowie dem restlichen Team von Nicer und SSPH+ für die herzlichen Stunden im Büro bedanken.

Für die produktive Zusammenarbeit und Unterstützung bei jedweden statistischen Fragen möchte ich mich vielmals bei Prof. Torsten Hothorn, Julia Meyer, Dr. Sarah Haile und Dr. Julia Braun bedanken. Und auch Dr. Matthias Bopp gilt mein Dank, der mir bei allfälligen Fragen weitergeholfen hat.

Herzlich danke ich Prof. Milo Puhan für seine fortwährende Unterstützung. Ich bedanke mich auch bei Dr. Eva Furrer und Emily Stone für die Organisation rund um das Doktoratsprogramm Epidemiologie und Biostatistik.

Mein tiefer Dank gilt meiner Mutter, die mich stets auf meinem akademischen Weg unterstützt hat. Danke, dass du mir dabei geholfen hast das Leben zu verstehen. Ich danke von Herzen meiner Grossmutter, die mir stets ein Vorbild war die Dinge selbst in die Hand zu nehmen und die kleinen Dinge des Alltages zu schätzen. Mein herzlicher Dank gilt auch meinem Bruder, der mir ein treuer Freund ist.

Abstract

Noncommunicable diseases (NCDs) are commonly characterized by not being passed from one person to another, being of long duration and slow progression. Premature mortality due to NCD is of major concern in low and middle-income countries as well as in high-income countries like Switzerland. Cardiovascular disease (CVD), cancer and chronic respiratory disease account for most of the NCD deaths worldwide. Whereas age-standardized rates declined between 1980 and 2015, the absolute number of NCD death increased e.g. due to a growing and aging world population. NCDs have individual risk factors, but share also common ones, e.g. behavioral factors such as smoking, environmental factors such as ambient particulate matter pollution, and hereditary factors. These risk factors are targets of NCD prevention, which can be classified as behavioral or structural and as primary, secondary, or tertiary, depending on the stage of disease development they are implemented at. Lifestyle factors offer great potential for the prevention of NCDs. Smoking, physical activity, diet, alcohol intake, and body composition were shown to be associated with NCD incidence and mortality. About 29% of cancer deaths were attributable to smoking in high-income countries in 2001 as well as 4% to alcohol and 3% to overweight and obesity. By investigating lifestyle factors individually their combined prevalence and distribution in the population is not captured. Furthermore, the coincident occurrence of multiple NCD risk factors has to be considered as likely. Aiming at understanding the lifestyle health outcome association, it is of importance to assess the impact of lifestyle patterns rather than of individual factors only. In the first paper presented, the association between mortality and lifestyle patterns was investigated by building a lifestyle score based on the cancer prevention recommendations of the WCRF/AICR 2007. The lifestyle score was shown to be associated with all-cause and cancer mortality. The lifestyle pattern of heavy smokers and obese individuals - two populations already being at high risk for adverse health outcomes - was examined in the second paper. Compared to normal-weight never smokers, heavy smokers and obese individuals were more likely to have an unhealthy lifestyle in general, whereby the association was stronger in heavy smokers. Working on this paper, the methodological issues arose how to deal with continuous outcome variables such as BMI in the analysis. This led to the third paper, in which we propose the novel approach of continuous logistic outcome regression to improve statistical analysis by using post hoc instead of ad hoc categorization of the outcome. This has the two main advantages of preventing information loss and improving

between-study comparability. The association between BMI and smoking was used as a case study. Another risk factor for NCD that was studied intensively is personality. However, evidence for an association is rather limited because of mixed results. The majority of studies focused on CVD and although an association was shown for e.g. hostility, the effect size was too small to identify public health relevance. The early findings, that type A personality is associated with CVD events were not supported by subsequent studies. For cancer, there is no evidence for an association with personality. Using different definitions and measurement instruments across studies to capture personality might have led to these mixed results, as well as not taking into account the individual components of the applied instrument. Targeting this latter aspect, we showed in the fourth paper that the components of the type A measurement instrument Bortner Scale, i.e. speed and competitiveness, were associated with mortality, but not the entire Bortner Scale. To conclude, lifestyle patterns were shown to be of major importance for the prevention of NCDs. For personality the evidence is limited, however a more sophisticated analysis of applied instruments might enhance the understanding of its association with NCDs.

Zusammenfassung

Nichtübertragbare Krankheiten (NCD) sind im Allgemeinen dadurch gekennzeichnet, dass sie nicht von Person zu Person übertragen werden und chronisch verlaufen. In Ländern mit hohen Einkommen wie der Schweiz, aber auch in Ländern mit niedrigen bzw. mittleren Einkommen, sind NCDs von grösster Public Health Relevanz. Kardiovaskuläre Erkrankungen (CVD), Krebs und chronische Atemwegserkrankung verursachen die meisten NCD Todesfälle weltweit. Während der altersstandardisierter Anteil der NCDs zwischen 1980 und 2015 zurückgegangen ist, hat die Anzahl der Fälle durch eine wachsende und alternde Weltbevölkerung zugenommen. NCDs haben neben individuellen Risikofaktoren auch gemeinsame, z.B. Verhaltensweisen wie das Rauchen, Umweltbelastungen wie der Feinstaub, und genetische Veranlagungen. Die Prävention spielt bei der Reduzierung der Krankheitslast von NCDs eine wesentliche Rolle. Es wird dabei zwischen Verhaltens- und Verhältnisprävention unterschieden. Des Weiteren setzen die Massnahmen der Prävention bei verschiedenen Stufen des Krankheitsprozesses an, wonach primär, sekundär und tertiär Präventionen unterschieden werden. Lebensstil bietet ein grosses Potential für die Prävention von NCDs. Für Rauchen, körperlich Bewegung, Ernährung, Alkoholkonsum und Körperzusammensetzung wurde ein Zusammenhang mit der Inzidenz und Mortalität von NCDs gezeigt. In Ländern mit einem hohen Einkommen wurden 2001 etwa 24% der Krebstodesfälle dem Rauchen zugeschrieben, dem Alkohol 4% und dem Übergewicht einschliesslich der Adipositas 3%. Einzelne Lebensstilfaktoren zu untersuchen vernachlässigt jedoch, dass Risikofaktoren kombiniert auftreten und somit das tatsächliche Risiko für NCD nicht geschätzt wird. Um die Beziehung zwischen Lebensstil und Gesundheit zu verstehen ist es wichtig, ebenso den Einfluss von Lebensstilmustern zu untersuchen und nicht nur den von einzelnen Risikofaktoren. Im ersten Paper der vorliegenden Arbeit wurde die Assoziation zwischen Mortalität und Lebensstilmustern anhand eines Lebensstil Scores untersucht, welcher basierend auf den Empfehlungen zur Krebsprävention des WCRF/AICR gebildet wurde. Es hat sich gezeigt, dass dieser Lebensstil Score mit Sterblichkeit insgesamt und Krebssterblichkeit assoziiert war. Die Lebensstilmuster von starken Rauchern und Adipösen - zwei Populationen die bereits ein erhöhtes gesundheitliches Risiko durch den entsprechenden Risikofaktor haben – wurden im zweiten Paper untersucht. Verglichen mit normalgewichtigen Nichtrauchern neigten starke Raucher und Adipöse zu einem insgesamt ungesünderen Lebensstil, wobei die Assoziation für starke Raucher stärker war. Bei der Erstellung dieses

Papers kam die Frage auf, wie kontinuierliche abhängige Variablen (z.B. BMI) ausgewertet werden sollen. Diese Fragestellung führte zum dritten Paper. In diesem wurde der neue Ansatz der continuous outcome logistic regression vorgestellt und empirisch evaluiert. Bei diesem Ansatz wird die abhängige Variable nach der statistischen Analyse kategorisiert und nicht, wie derzeit gängige epidemiologische Praxis, vor der Analyse. Dies hat zwei wesentliche Vorteile, zum einen wird ein Informationsverlust durch die vorzunehmende Kategorisierung verhindert und zum anderen wird die Vergleichbarkeit zwischen Studien verbessert, indem auch Studien mit unterschiedlicher Kategorisierung der abhängigen Variable verglichen werden können. Die Assoziation zwischen BMI und Rauchen wurde hierfür als Fallstudie verwendet. Ein weiterer NCD Risikofaktor der intensiv untersucht wurde ist Persönlichkeit. Die meisten Studien zum Einfluss von Persönlichkeit auf NCD wurden zu CVD durchgeführt. Die Evidenz für eine Assoziation ist jedoch limitiert durch sich widersprechende Studienergebnisse. Beispielsweise wurde die Rolle von Feindseligkeit untersucht, hierbei konnte ein Zusammenhang gezeigt werden. Allerdings war dieser zu gering, um Public Health Relevanz zu erreichen. Des Weiteren hatten Ergebnisse früherer Studien zu CVD und Typ A Persönlichkeit eine Assoziation gezeigt, allerdings konnte diese durch spätere Studien nicht bestätigt werden. Für Krebs ist keine Evidenz für einen Zusammenhang mit Persönlichkeit vorhanden. Mögliche Erklärungen für diese sich widersprechenden Ergebnisse bzw. Nullergebnisse sind das Verwenden von unterschiedlichen Messinstrumenten und deren Analyse nach Gesamtskala. Um letzteren Aspekt genauer zu untersuchen, wurde im vierten Paper die Bortner Skala, ein Instrument zur Erfassung von Typ A Persönlichkeit, gesamt sowie nach ihren Subskalen Wettbewerbsfähigkeit und Geschwindigkeit untersucht. Dabei hat sich gezeigt, dass die Bortner Skala gesamt nicht mit Mortalität assoziiert war, aber ihre Subskalen. Zusammenfassend hat sich gezeigt, dass das Betrachten von Lebensstilmustern äusserst wichtig zur erfolgreichen Prävention von NCDs ist. Hingegen ist die Rolle von Persönlichkeit in der NCD Prävention noch unzureichend untersucht, aber die Anwendung von genaueren Analysen zur Auswertung der angewendeten Messinstrumente kann zukünftig dazu beitragen ein besseres Verständnis zu gewinnen.

Thesis Outline

Introduction

Thesis summary

Annex

Paper I **Adherence to the cancer prevention recommendations of the WCRF/AICR and mortality: a census-linked cohort**
Tina Lohse, David Faeh, Matthias Bopp, Sabine Rohrmann for the Swiss National Cohort Study Group.
Published in the American Journal of Clinical Nutrition. 2016.104(3):678–85.

Paper II **Heavy Smoking Is More Strongly Associated with General Unhealthy Lifestyle than Obesity and Underweight**
Tina Lohse, Sabine Rohrmann, Matthias Bopp, David Faeh
Published in PLoS ONE. 2016.11(2):1–13.

Paper III **Continuous Outcome Logistic Regression for Analyzing Body Mass Index Distributions**
Tina Lohse, Sabine Rohrmann, David Faeh, Torsten Hothorn
Under Review

Paper IV **Type A personality and mortality: Competitiveness but not speed is associated with increased risk**
Tina Lohse, Sabine Rohrmann, Aline Richard, Matthias Bopp, David Faeh for the Swiss National Cohort Study Group
Published in Atherosclerosis. 2017. 262:19-24.

Introduction

Public health relevance of cancer and other noncommunicable diseases

Noncommunicable diseases (NCDs) are commonly characterized by not being passed from one person to another, being of long duration and slow progression (1). NCD were estimated to account for 71.3% of deaths worldwide (39. 8 million) in 2015. Communicable, maternal, neonatal, and nutritional diseases (20.2% deaths, 11.3 million) were in second and injuries (8.5%, 4.7 million) in third place. The absolute number of NCD deaths increased since 2005 by 14.3%, but age-standardized rates declined in the same time period from 719.1 to 624.7 per 100 000 (2). This corresponds to 21 062.4 per 100 000 disability adjusted life years due to NCD in 2015 (3). NCD are not only of major concern in high-income countries, about 80% of premature deaths due to NCD occur in low and middle-income countries (1). NCD gained public health relevance in the past, because of an aging world population and decreasing rates of communicable, maternal, neonatal, and nutritional diseases (2). Globally, the life expectancy increased between 1980 and 2015 from 59.6 years in males and 63.7 years in females to 69.0 years and 74.5, respectively. The decrease in the rate of communicable, maternal, neonatal, and nutritional diseases was estimated to be 19.7% (absolute) and 29.6% (age-standardized) (2).

Cardiovascular disease (CVD), cancer, and chronic respiratory diseases account for most of NCD deaths (17.9 million, 8.8, 3.8) (2). The leading cause of death worldwide is CVD (4). For both CVD and cancer the absolute number of deaths increased, but the age-standardized rates declined in accordance with the overall NCD trend (2).

Deaths contributing to CVD mortality rose from 2005 to 2015 by 12.5%, given a decreasing age-standardized rate of 15.6%. The development was similar for ischemic heart disease (IHD) and stroke as they accounted for 85.1% of all CVD deaths in 2015. Deaths due to IHD rose by 16.6% since 2005. Age-standardized rates declined for both stroke (21.0%) and IHD (12.8%) (2). Between 2005 and 2015, the absolute number of cases increased strongest in cancer mortality (17.0%); at the same time the age-standardized rate decreased by 10.0%.

Tracheal, lung, and bronchus were the leading cancer types with regard to mortality (absolute number and age-standardized rates). Their number increased until 2015 by more than 20%; a development that can also be observed for colon, rectum, malignant skin melanoma, pancreatic, prostate, breast, and ovarian cancer. Strongest declines in death rates were observed for esophageal cancer (26.8%) and Hodgkin`s lymphoma (23.9%) (2).

The same pattern of age-standardized rates as for CVD was reported for the two leading chronic respiratory diseases, i.e. chronic obstructive pulmonary disease (COPD, 22.9%) and asthma (31.3%). Whereas their absolute numbers did not changed considerably between 2005 and 2015 (2).

In Switzerland, a high-income country, NCD were estimated to account for 91% of deaths in 2014. Cardiovascular diseases contributed 35%, cancers 27%, and respiratory diseases 4% to total deaths. Corresponding age-standardized rates were decreasing over the past decade, especially in CVD and cancer. The probability of dying premature, i.e. between 30 and 70 years of age, was about 9% (5,6). In Switzerland 2013, the age-standardized mortality rates of IHD, stroke, lung cancer and respiratory diseases were lower than the European average (7).

Causes of noncommunicable diseases

NCDs have multiple modifiable risk factors (8). Cancer, CVD and chronic respiratory disease have individual risk factors, but share also common ones. These are for example, behavioral factors like smoking, or environmental factors like ambient particulate matter pollution and household air pollution from solid fuels, as well as hereditary factors (4,8–11). The role of chance in the development of cancer is also discussed, based on the notion that each stem cell division induces the risk of random mutations, which may lead to epigenetic changes (10,12,13).

Terminology of prevention

The World Health Organization (WHO) defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (14). Hence, “the highest attainable standard of health is one of the fundamental rights of every human being”. The disciplines health promotion, public health and medicine are targeting health, but indeed rely on different concepts of health, which are complementary (15). Health promotion is focusing on resources that keep individuals healthy using the salutogenic approach. Public

Health pursues to promote health as well, but geared towards populations by applying organized community efforts (15). Medicine aims to recover health after disease occurred, i.e. to cure disease or reduce symptoms to prolong a high quality of life. These disciplines share the concept of prevention, according to their respective focus. Prevention has the objective to avert the development of disease and preservation of the current health status, respectively (16). Primary, secondary and tertiary prevention measures are differentiated, depending on at which stage of disease development the measure is implemented (17). Primary prevention is applied in healthy individuals to protect them from disease development and manifestation of clinical symptoms. This is achieved by reducing risks in general, either on a population or individual level, e.g. by vaccination or provision of healthy meals in schools or workplace health promotion. Secondary prevention comprises the early detection of disease, taking into account known risk factors, i.e. screening of risk populations. Measures of secondary prevention are for example the screening for breast cancer, newborn screening and health check-ups by the general practitioner. Tertiary prevention starts when disease is diagnosed and targets at the prevention of the chronification and secondary disease. Examples of tertiary prevention are chronic disease management programs, care of cancer survivors, and rehabilitation (15–17). Another dimension of classifying preventive measures is the characteristic whether they are behavioral or structural. Behavioral measures aim to change the behavior of individuals or groups, whereas structural measures target the change of structures by the influence of other fields, which are not directly related to the health sector, e.g. city planning, public transportation and tax system (16,17).

Chances and challenges in the prevention of noncommunicable diseases

The reduction of the overall lung cancer incidence in western countries like the United States, Germany, and Switzerland is a successful example of NCD prevention (18). Established smoking control strategies, including campaigns, smoking bans, high taxes for tobacco products, and consulting of patients by general practitioners seem to be effective. Nevertheless, these efforts have to be intensified. Although the overall lung cancer incidence is decreasing, the incidence in women is increasing in respective countries (18). Vaccines were also shown to be highly effective to reduce liver cancer caused by Hepatitis B (19,20) and cervical cancer caused by HPV (21). One of the most prominent examples for successful CVD prevention is the North Karelia Project started in 1972 (22). A comprehensive community-based intervention was applied, involving multiple players like health services,

NGO's, industry, media and public policy. Within 40 years, in the 35- to 64-year-old male population the age-adjusted coronary heart disease mortality was reduced by 84% (22).

The prevention of NCD offers the chance to reduce the burden of disease in the population considerably. The decline in most age-standardized NCD death rates is due to a reduction of known risk factors in the population and improvements in early detection and therapy (2). Especially for CVD, significant biomarkers such as hypertension (23) were identified to allow for the development of chemopreventive agents targeting the treatment of early disease (24). For cancer the treatment of early stages is particularly important to increase the chance of cure or prolonged and high-quality life. So far, this is much more difficult to realize for cancer, than for CVD (24). Most cancers are detected and treated too late (9). A lot of effort has been put into the cure of advanced disease, rather than early disease prevention and health promotion (24). The broader application of chemoprevention in the field of cancer is a matter of ongoing research (25,26).

In general, it remains a challenging task to implement effective measures for the prevention of NCDs (24,27,28). Therefore, it is required that capacity building in public health and the translation of scientific findings into practice, i.e. evidence-based public health, is encouraged (29). The United Nations has drawn the attention of governmental leaders to NCDs worldwide. In 2013, the 66th General Assembly of the UN adopted a declaration, which requests the international community and its member states to further intensify their efforts in the prevention and control of NCDs (30). The WHO released a Global status as well as European progress report (31,32) and based on that a Global Action Plan in 2014 (33). For the European Region an Action Plan was already set in 2011 (34). Since 2017, in Switzerland a national NCD strategy has been implemented (6).

Lifestyle factors and their potential for prevention of noncommunicable diseases

Lifestyle factors offer great potential for the prevention of NCDs (35). Smoking, physical activity, diet, alcohol intake as well as body composition, most often measured using the Body Mass Index (BMI), are associated with NCDs (36–38). Ford et al. showed that the risk for all-cause mortality was reduced due to non-smoking by 56%, physical activity by 47%, and healthy diet by 26% (37).

For cancer, it was shown that the importance of risk factors differed between high and low-and-middle income countries (9). In high-income countries such as Switzerland, smoking, alcohol, overweight and obesity are the most important lifestyle risk factors. It was estimated

that in 2001 about 29% of cancer deaths in high-income countries were attributable to smoking as well as 4% to alcohol and 3% to overweight and obesity. The leading risk factors in low-and-middle income countries were smoking and alcohol as well, but also low fruit and vegetable consumption. In low-and-middle income countries 18% of cancer deaths are attributable to smoking, 4% to alcohol and 6% to low fruit and vegetable consumption (9). The traditional risk factors for CVD worldwide are hypertension, physical inactivity, high BMI, smoking as well as diabetes. In Eastern Europe, hazardous alcohol consumption is additionally of major importance (4). In an US sample from 1996-1998, the population attributable fraction was estimated to be 25% for hypertension, 17% for diabetes, 6% for obesity, 13% for smoking, and 9% for hypercholesterolemia (39). Except for the latter, the population attributable fraction (PAF) was shown to be rather stable over time. The PAF for hypercholesterolemia was reduced by 50% since 1987-1989. For COPD and asthma, two major chronic respiratory diseases, smoking as well as underweight and obesity are important lifestyle risk factors (40,41). It was shown that smoking is the major risk factor for COPD, but the estimated PAF based on cohort study data vary rather widely between 39.6% and 76.2% (42).

Prevalence of lifestyle risk factors

The prevalence of lifestyle risk factors in adults varies by region. For example, in countries such as Armenia, Russia and Indonesia the smoking prevalence exceeded more than 50% in men in 2012. On the other hand in Antigua and Barbuda, Dominica and Ethiopia the smoking prevalence in men was less than 10% (43). In Switzerland the prevalence was estimated for 2012 to be 32% in men and 24% in women (44). Between 1980 and 2012, the global age-standardized prevalence of smoking decreased from 41.2% to 31.1% in men and from 10.6% to 6.2% in women (43), but due to world population growth the absolute number of smokers increased (43). Non-smoking is strongly recommended (45), and it is important to combine cessation programs with weight control intervention to maximize induced health benefits (46).

Harmful use and alcohol dependency were estimated to be prevalent in 1.8% and 2.3% of the world population, respectively (47). In the WHO European Region, their prevalence was highest in Russia (3.5%) and the Ukraine (4.0%). In these countries the most risky drinking patterns were observed. For alcohol use and related harms, it was observed that the difference between men and women regarding prevalence was decreasing (48). Men born in the early

1900 were 3.6 times more likely to experience alcohol-related harms than women. In birth cohorts of the late 1990 the corresponding risk was reduced to 1.3 in men compared to women (48). In Switzerland 2012, 14% of the population shows an alcohol consumption that induces health risks, either through chronic-high alcohol consumption (5%) or binge drinking (11%) (44). The recommendations for alcohol consumption differ by NCD. To prevent cancer alcohol abstinence is recommended (45). The recommendation on low-risk drinking differs by country (49). If alcohol is consumed, the American Heart Association recommends limiting the daily average of one to two drinks for men and one drink per day for women(50). One drink for example corresponds for example to 12 oz. beer (50).

Between 1980 and 2013, the combined global prevalence of overweight and obesity increased from 28.8% to 36.9% in men and from 29.8% to 38.0% in women (51). In both, developed and developing countries the prevalence has increased, but differs by sex. In developed countries overweight and obesity were more prevalent in men, whereas in developing countries this was the case for women. In 2013, obesity prevalence exceeded 50% for men in Tonga and for women e.g. in Kuwait and Kiribati (51). In Switzerland 2014/15, the prevalence of overweight was estimated to be 41.6% in men and 19.6% in women; the prevalence of obesity was 13.9% in men and 11.6% in women (52). The recommendation on healthy weight is staying in a normal-weight range (45), i.e. having a BMI between ≥18.5 and <25 (53).

Global estimates on general dietary behavior and low fruit and vegetable consumption in particular are rather rare. Hall et al. estimated that the prevalence of low fruit and vegetable consumption was 78.0%, using a data set including mainly low- and middle-income countries (2002-2003) (54). The prevalence was estimated to be lowest in Ghana (37.3%) and highest in Pakistan (99.3%) (54). For Switzerland low fruit and vegetable consumption was prevalent in 87% of the population, nevertheless only 13% did not include fruits and vegetables in their daily routine (2014-2015) (55). Low fruit and vegetable consumption is defined as not adhering to the “5 a day” recommendation of the WHO, which targets the consumption of 400g of fruit and/or vegetables (56). The WCRF released further recommendations on diet, e.g. limit the consumption of energy-dense foods and red meat, avoid processed meat and eat mostly foods of plat origin (45).

The WHO estimated that 23% of the world population was physically inactive in 2010 (31). The prevalence was higher in women (27%) than in men (20%). Furthermore, it was shown that physical inactivity was more prevalent in high-income countries (33%), compared to low-

income countries (17%). The highest prevalence was observed for the WHO Eastern Mediterranean Region (31%) and Region of the Americas (32%). The WHO defines physical inactivity as having less than 150 minutes of moderate-intensity physical activity per week, or equivalent (31). In Switzerland 2012, 27.5% of the population was physically inactive and consistent with the world population more women (30.9%) were inactive than men (24.1%) (57). These estimates are based on the Swiss recommendation on physical activity, which differs from the WHO recommendation by recommending 2.5 hours per week of moderate intensity or 1.25 hours per week of vigorous intensity to be physically active (57).

Lifestyle risk factors and their combined impact: from single lifestyle factors to lifestyle patterns

Investigating lifestyle risk factors individually, does not display their combined prevalence, distribution and impact on the population. But the coincident occurrence of multiple lifestyle risk factors for NCDs is likely (58–60). Reporting of multiple risk factors was shown to be associated with low educational level and health deterioration as well as having a chronic disease (58–61). The strongest association between lifestyle factors was shown for smoking and alcohol intake (59). De Vries et al. identified three clusters, i.e. the healthy, the unhealthy, and the poor nutrition cluster (61). Hence, lifestyle risk factors act synergistically in the development of NCD (4,11,35,38,62–64). To better understand the lifestyle-health outcome association, it is of importance to assess the impact of lifestyle patterns rather than of individual lifestyle factors only.

Several studies investigated the association between a combination of lifestyle risk factors, i.e. lifestyle patterns, and different health outcomes. Loef et al. performed a meta-analysis based on 21 studies to investigate the combined effect of healthy lifestyle factors on all-cause mortality (65). Their results showed a decrease in the hazard of all-cause mortality proportional to the number of protective factors. The combined prevalence of 4 out of 5 healthy lifestyles, i.e. normal-weight, low alcohol consumption, non-smoking, healthy diet, and sufficient physical activity, led to a reduction by 66% in all-cause mortality (65). These findings were further strengthened by subsequent studies (37,66–68), taking into account different populations, e.g. elderly (66) and Asian (67,68). Adherences to national recommendations on healthy lifestyle have been linked to reduced mortality (62,69). For cancer incidence and mortality, a protective association with healthy lifestyle was shown as well (62,70–75). Dartois et al. estimated that complying to common recommendations on

smoking, BMI, alcohol intake, fruit and vegetable consumption, and physical activity can prevent 6.3% of total cancers and 47.5% of lung cancers (70). To estimate the influence of healthy lifestyle on cancer besides smoking, several studies focused on the combined impact of the other mentioned lifestyle factors (71,72,74,75). Hereto, Romaguera et al. showed that adherence to the WCRF/AICR recommendations was associated with reduced risk of cancer, i.e. comparing participants with the highest level of adherence with those having the lowest led to 0.84 HR (95% CI 0.72, 0.99) in men and 0.81 (0.72, 0.91) in women (72). Similar protective associations have been observed for healthy lifestyle and CVD incidence as well as mortality (62,69,76–78). Carlsson et al. showed that having a healthy lifestyle, i.e. combined non-smoking, low alcohol intake, moderate physical activity at least once a week and a healthy diet was associated with reduced CVD incidence; independent of BMI (79). Mitchell et al. investigated the association between lifestyle pattern and CVD mortality (78). They found that a combination of at least 2 of the following lifestyle factors decreased the risk of CVD mortality (0.67 HR (95% CI 0.49,0.91): cardiorespiratory fitness, normal BMI, physically activity and non-smoking (78). Using the cancer prevention recommendations of the WCRF/AICR (45) and therefore not including the effect of smoking on CVD incidence or mortality showed also a protective association with healthy lifestyle factors (69).

Personality traits and their potential for prevention of noncommunicable diseases

The association between personality traits and mortality as well as NCD incidence has been widely studied. However, evidence for an association is rather limited. Studies investigated the association for different concepts of personality, e.g. individual traits, big five (extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience (80)), type A (an individual's behavior is characterized by ambitiousness, competitiveness, easily aroused hostility, impatience and an exaggerated sense of time urgency (81)) and type D (an individual's behavior is characterized by the general tendency towards emotional distress characterized by high scores on social inhibition and negative affectivity traits (82)). For total mortality, only low conscientiousness was shown to be a risk factor across studies (83,84). Nabi et al. additionally observed an association with neurotic hostility (85). Other personality traits such as extraversion, neuroticism or dominance as well as type D and A personality were not associated with total mortality (86–90). The vast majority of studies on personality and its associations with health outcomes focused on CVD incidence and mortality. These studies showed the relevance of different concepts of personality. Individual

personality traits have been linked to CVD outcomes like anger and hostility (83,91–94), openness (95), and neuroticism (88). Nonetheless, there is also contradicting evidence (92). For example, Batty et al. did not confirm an association of extraversion or neuroticism with mortality (87). A meta-analysis observed an association with hostility, but the estimated effect size was very small and they concluded that it does not raises public health relevance (94). Jokela et al. investigated the association between personality traits by the main cardiac and cerebral disease outcomes (96). They showed that the risk for stroke and not coronary heart disease mortality was increased in individuals with higher extraversion. For high neuroticism the findings were opposite. High conscientiousness was associated with lower risk of mortality in both of the outcomes (96). Type A personality was first linked to CVD outcomes in the 1970s (97–100). However, subsequent studies did not confirm the indicated association (94,101–105). Gallacher et al. conclude in their study on incidence CVD events and type A personality that one can predict when an event will occur rather than whether it will occur (106). As an explanation, they suggest that type A personality increases the risk of being exposed to potential triggers, rather than affecting the process of atherosclerosis (106). In meta-analyses type D personality was shown to be relevant for the prognosis in CVD patients (107), although the estimated effect was declining over time (108). Kupper et al. concluded that type D personality was associated with an increased risk of cardiac events in coronary artery disease patients, but not with non-cardiac mortality or with events in individuals aged ≥70 years (82). No significant association was observed between type D personality and coronary heart disease incidence (109). For cancer the evidence is much weaker, most studies did not show an association. Neither for the personality traits of the big five (87,88,110,111), nor for type A personality (112). Ranchor et al. summarized the existing evidence on cancer and personality by stating if an association exists at all, one can be confident that the overall effect size is much too small to have clinical and public health relevance (113). The same applies for respiratory diseases (87,88).

Chapman et al. investigated the role of socioeconomic status and lifestyle factors in the association between personality and all-cause mortality (114). They showed modest associations between socioeconomic status (SES) and the big 5. Personality explained about 20% of the SES gradient in all-cause mortality, while SES explained 8% of personality-induced risk. Furthermore, they found that lifestyle factors explained the SES and personality induced risk; besides remaining residual risk (114). Several studies support this finding by

showing that personality and lifestyle risk factors are associated, e.g. physical activity (115,116), smoking (80,117), and diet (118–120).

In conclusion, modifiable factors such as lifestyle are important targets of preventive measures to reduce the burden of NCD. Moreover, their association with health outcomes is not yet fully understood and the potential for prevention is still unexhausted.

References

1. World Health Organization. Noncommunicable diseases, fact sheet [Internet]. WHO. 2016. Available from: http://www.who.int
2. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459–544.
3. Kassebaum NJ, Arora M, Barber RM, Bhutta ZA, Brown J, Carter A, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1603–58.
4. Benziger CP, Roth GA, Moran AE. The Global Burden of Disease Study and the Preventable Burden of NCD. Glob Heart. 2016;11(4):393–7.
5. World Health Organisation. WHO Non-communicable diseases, Country profiles, Switzerland [Internet]. 2014. Available from: http://www.who.int
6. Nationale Strategie Prävention nichtübertragbarer Krankheiten (NCD-Strategie) 2017-2024 [Internet]. Bern; 2016. Available from: https://www.bag.admin.ch
7. OECD/EU. Health at a Glance: Europe 2016 - State of Health in the EU Cycle [Internet]. Paris: OECD Publishing; 2016. (Health at a Glance: Europe). Available from: http://dx.doi.org/10.1787/9789264265592-en
8. Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1659–724.
9. Danaei G, Vander Hoorn S, Lopez AD, Murray CJL, Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366(9499):1784–93.
10. Luzzatto L, Pandolfi PP. Causality and Chance in the Development of Cancer. N Engl J Med. 2015;373(1):84–8.

11. Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. Int J Tuberc Lung Dis. 2015;19(1):10–20.

12. Tomasetti C, Vogelstein B. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science. 2015;347(6217):78–81.

13. Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science. 2017;355(6331):1330–4.

14. Preamble to the Constitution of WHO as adopted by the International Health Conference [Internet]. New York, 19 June - 22 July 1946, signed on 22 July 1946 by the representatives of 61 States (Official Records of WHO, no. 2, p. 100) and entered into force on 7 April 1948; Available from: http://www.who.int

15. Jekel JF, Katz DL, Elmore JG, Wild DMG. Epidemiology, Biostatistics, and Preventive Medicine. 3rd ed. Jekel JF, Katz DL, Elmore JG, Wild DMG, editors. Philadelphia, PA: Saunders/Elsevier; 2007.

16. Hüter-Becker A, Dölken M, editors. Prävention. Stuttagrt: Thieme; 2008.

17. Leitbegriffe der Gesundheitsförderung und Prävention. Köln: Bundeszentrale für gesundheitliche Aufklärung; 2011.

18. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-tieulent J, Jemal A. Global Cancer Statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.

19. Chang M-H. Cancer prevention by vaccination against hepatitis B. Recent Results Cancer Res. 2009;181:85–94.

20. Blumberg BS. Hepatitis B virus and the control of hepatocellular carcinoma. IARC Sci Publ. 1984;(63):243–61.

21. Heffernan ME, Garland SM, Kane MA. Global reduction of cervical cancer with human papillomavirus vaccines: insights from the hepatitis B virus vaccine experience. Sex Health. 2010;7(3):383.

22. Puska P. Why Did North Karelia—Finland Work?: Is it Transferrable? Glob Heart. 2016;11(4):387–91.

23. Vasan RS. Biomarkers of Cardiovascular Disease: Molecular Basis and Practical Considerations. Circulation. 2006;113(19):2335–62.

24. Sporn MB. The war on cancer. Lancet. 1996;347(9012):1377–81.

25. Meyskens FL, Mukhtar H, Rock CL, Cuzick J, Kensler TW, Yang CS, et al. Cancer Prevention: Obstacles, Challenges and the Road Ahead. J Natl Cancer Inst. 2016;108(2).

26. Perloff M, Steele VE. Early-phase development of cancer prevention agents: challenges and opportunities. Cancer Prev Res (Phila). 2013;6(5):379–83.

27. Mendis S, Chestnov O. The Global Burden of Cardiovascular Diseases: A Challenge to Improve. Curr Cardiol Rep. 2014;16(5):486.

28. Piepoli MF, Corrà U, Abreu A, Cupples M, Davos C, Doherty P, et al. Challenges in secondary prevention of cardiovascular diseases: A review of the current practice. Int J Cardiol. 2015;180:114–9.

29. Diem G, Brownson R, Grabauskas V, Shatchkute A, Stachenko S. Prevention and control of noncommunicable diseases through evidence-based public health: implementing the NCD 2020 action plan. Glob Heal Promot. 2016;23(3):5–13.

30. General Assembly resolution 66/2, Political Declaration of the High-level Meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases, A/RES/66/2. (19 September 2011) [Internet]. Available from: http://www.un.org

31. World Health Organization. Global status report on noncommunicable diseases 2014 [Internet]. Geneva; 2014. Available from: http://apps.who.int

32. World Health Organization Regional Office for Europe. Prevention and Control of Noncommunicable diseases in the European Region: a progress report [Internet]. Geneva; 2014. Available from: http://www.euro.who.int

33. World Health Organisation. Global Action Plan for the Prevention and Control of NCDs 2013-2020 [Internet]. Geneva: World Health Organization; 2015. Available from: http://apps.who.int

34. World Health Organisation Regional Office for Europe. Action plan for implementation of the European Strategy for the Prevention and Control of Noncommunicable Diseases 2012 – 2016 [Internet]. Vol. 6. 2011. Available from: http://apps.who.int

35. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. Arch Intern Med. 2010;170(8):711–8.

36. Behrens G, Fischer B, Kohler S, Park Y, Hollenbeck AR, Leitzmann MF. Healthy lifestyle behaviors and decreased risk of mortality in a large prospective study of U.S. women and men. Eur J Epidemiol. 2013;28(5):361–72.

37. Ford ES, Bergmann MM, Boeing H, Li C, Capewell S. Healthy lifestyle behaviors and all-cause mortality among adults in the United States. Prev Med. 2012;55(1):23–7.

38. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. BMJ. 2008;337:a1440.

39. Cheng S, Claggett B, Correia AW, Shah AM, Gupta D, Skali H, et al. Temporal Trends in the Population Attributable Risk for Cardiovascular Disease: The Atherosclerosis Risk in Communities Study. Circulation. 2014;130(10):820–8.

40. Halldin CN, Doney BC, Hnizdo E. Changes in prevalence of chronic obstructive pulmonary disease and asthma in the US population and associated risk factors. Chron Respir Dis. 2015;12(1):47–60.

41. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? Lancet. 2015;386:1075–85.

42. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2010;182:693–718.

43. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA. 2014;311(2):183–92.

44. Bundesamt für Statistik. Schweizerische Gesundheitsbefragung 2012 [Internet]. Neuchâtel; 2013. Available from: https://www.bfs.admin.ch

45. World Cancer Research Fund, American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. [Internet]. Washington, DC; 2007. Available from: http://www.aicr.org

46. Chinn S, Jarvis D, Melotti R, Luczynska C, Ackermann-Liebrich U, Antó JM, et al. Smoking cessation, lung function, and weight gain: a follow-up study. Lancet. 2005;365(9471):1629-35-1.

47. Global status report on alcohol and health 2014 [Internet]. Geneva; 2014. Available from: http://apps.who.int

48. Slade T, Chapman C, Swift W, Keyes K, Tonks Z, Teesson M. Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: systematic review and metaregression. BMJ Open. 2016;6(10):e011827.

49. Kalinowski A, Humphreys K. Governmental standard drink definitions and low-risk alcohol consumption guidelines in 37 countries. Addiction. 2016;111(7):1293–8.

50. American Heart Association. Alcohol and Heart Health [Internet]. Available from: http://www.heart.org

51. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766–81.

52. Bundesamt für Lebensmittelsicherheit und Veterinärwesen, Bundesamt für Gesundheit. Body Mass Index (BMI) in der Schweiz 2014/15 [Internet]. 2017. Available from: https://www.bag.admin.ch

53. World Health Organisation. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. [Internet]. Geneva; 2000. Available from: www.whqlibdoc.who.int

54. Hall JN, Moore S, Harper SB, Lynch JW. Global Variability in Fruit and Vegetable Consumption. Am J Prev Med. 2009;36(5):402–409.e5.

55. Bundesamt für Lebensmittelsicherheit und Veterinärwesen. Früchte- und Gemüsekonsum in der Schweiz 2014/15 [Internet]. 2015. Available from: https://www.blv.admin.ch

56. WHO. Diet, nutrition and the prevention of chronic diseases [Internet]. Vol. 916, World Health Organization technical report series. 2003. Available from: http://eutils.ncbi.nlm.nih.gov

57. Mattli R, Hess S, Maurer M, Eichler K, Pletscher M, Wieser S. Kosten der körperlichen Inaktivität in der Schweiz Schlussbericht [Internet]. 2014. Available from: https://www.zhaw.ch

58. Hausdorf K, Eakin E, Whiteman D, Rogers C, Aitken J, Newman B. Prevalence and correlates of multiple cancer risk behaviors in an Australian population-based survey: results from the Queensland Cancer Risk Study. Cancer Causes Control. 2008;19(10):1339–47.

59. Schuit AJ, van Loon AJM, Tijhuis M, Ocké MC. Clustering of Lifestyle Risk Factors in a General Adult Population. Prev Med. 2002;35(3):219–24.

60. Pronk NP, Anderson LH, Crain AL, Martinson BC, O'Connor PJ, Sherwood NE, et al. Meeting recommendations for multiple healthy lifestyle factors. Prevalence, clustering, and predictors among adolescent, adult, and senior health plan members. Am J Prev Med. 2004;27(2 Suppl):25–33.

61. de Vries H, van 't Riet J, Spigt M, Metsemakers J, van den Akker M, Vermunt JK, et al. Clusters of lifestyle behaviors: results from the Dutch SMILE study. Prev Med. 2008;46(3):203–8.

62. Petersen KEN, Johnsen NF, Olsen A, Albieri V, Olsen LKH, Dragsted LO, et al. The combined impact of adherence to five lifestyle factors on all-cause, cancer and cardiovascular mortality: a prospective cohort study among Danish men and women. Br J Nutr. 2015;113(5):849–58.

63. Lee C-D, Sui X, Hooker SP, Hébert JR, Blair SN. Combined impact of lifestyle factors on cancer mortality in men. Ann Epidemiol. 2011;21(10):749–54.

64. Khaw K-T, Wareham N, Bingham S, Welch A, Luben R, Day N. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. PLoS Med. 2008;5(1):e12.

65. Loef M, Walach H. The combined effects of healthy lifestyle behaviors on all cause mortality: a systematic review and meta-analysis. Prev Med. 2012;55(3):163–70.

66. Martin-Diener E, Meyer J, Braun J, Tarnutzer S, Faeh D, Rohrmann S, et al. The combined effect on survival of four main behavioural risk factors for non-communicable diseases. Prev Med. 2014;65:148–52.

67. Yun JE, Won S, Kimm H, Jee SH. Effects of a combined lifestyle score on 10-year mortality in Korean men and women: a prospective cohort study. BMC Public Health. 2012;12:673.

68. Nechuta SJ, Shu X-O, Li H-L, Yang G, Xiang Y-B, Cai H, et al. Combined impact of lifestyle-related factors on total and cause-specific mortality among Chinese women: prospective cohort study. PLoS Med. 2010;7(9).

69. Vergnaud A-C, Romaguera D, Peeters PH, van Gils CH, Chan DSM, Romieu I, et al. Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: results from the European Prospective Investigation into Nutrition and Cancer cohort study. Am J Clin Nutr. 2013;97(5):1107–20.

70. Dartois L, Fagherazzi G, Boutron-Ruault M-C, Mesrine S, Clavel-Chapelon F. Association between five lifestyle habits and cancer risk: results from the E3N cohort. Cancer Prev Res. 2014;7(5):516–25.

71. Hastert TA, Beresford SAA, Sheppard L, White E. Adherence to the WCRF/AICR cancer prevention recommendations and cancer-specific mortality: results from the Vitamins and Lifestyle (VITAL) Study. Cancer Causes Control. 2014;25(5):541–52.

72. Romaguera D, Vergnaud A-C, Peeters PH, van Gils CH, Chan DSM, Ferrari P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr. 2012;96(1):150–63.

73. Cerhan JR, Potter JD, Gilmore JME, Janney CA, Kushi LH, Lazovich D, et al. Adherence to the AICR cancer prevention recommendations and subsequent morbidity and mortality in the Iowa Women's Health Study cohort. Cancer Epidemiol Biomarkers Prev. 2004;13(7):1114–20.

74. Thomson CA, McCullough ML, Wertheim BC, Chlebowski RT, Martinez ME, Stefanick ML, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. Cancer Prev Res (Phila). 2014;7(1):42–53.

75. Kabat GC, Matthews CE, Kamensky V, Hollenbeck AR, Rohan TE. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. Am J Clin Nutr. 2015;101(3):558–69.

76. McCullough ML, Patel A V, Kushi LH, Patel R, Willett WC, Doyle C, et al. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. Cancer Epidemiol Biomarkers Prev. 2011;20(6):1089–97.

77. Odegaard AO, Koh W-P, Gross MD, Yuan J-M, Pereira MA. Combined lifestyle factors and cardiovascular disease mortality in Chinese men and women: the Singapore Chinese health study. Circulation. 2011;124(25):2847–54.

78. Mitchell JA, Bornstein DB, Sui X, Hooker SP, Church TS, Lee CD, et al. The impact of combined health factors on cardiovascular disease mortality. Am Heart J. 2010;160(1):102–8.

79. Carlsson AC, Wändell PE, Gigante B, Leander K, Hellenius M-L, de Faire U. Seven modifiable lifestyle factors predict reduced risk for ischemic cardiovascular disease and all-cause mortality regardless of body mass index: a cohort study. Int J Cardiol. 2013;168(2):946–52.

80. Zvolensky MJ, Taha F, Bono A, Goodwin RD. Big five personality factors and cigarette smoking: A 10-year study among US adults. J Psychiatr Res. 2015;63:91–6.

81. Friedman M, Rosenman R. Type A behavior and your heart. New York: Alfred A. Knopf; 1974.

82. Kupper N, Denollet J. Explaining heterogeneity in the predictive value of Type D personality for cardiac events and mortality. Int J Cardiol. 2016;224:119–24.

83. Jokela M, Batty GD, Nyberg ST, Virtanen M, Nabi H, Singh-Manoux A, et al. Personality and all-cause mortality: individual-participant meta-analysis of 3,947 deaths in 76,150 adults. Am J Epidemiol. 2013;178(5):667–75.

84. Taylor MD, Whiteman MC, Fowkes GR, Lee AJ, Allerhand M, Deary IJ. Five Factor Model Personality Traits and All-Cause Mortality in the Edinburgh Artery Study Cohort. Psychosom Med. 2009;71(6):631–41.

85. Nabi H, Kivimäki M, Marmot MG, Ferrie J, Zins M, Ducimetière P, et al. Does personality explain social inequalities in mortality? The French GAZEL cohort study. Int J Epidemiol. 2008;37(3):591–602.

86. André M, Billstedt E, Bengtsson C, Hällström T, Lissner L, Skoog I, et al. Personality in women and associations with mortality: a 40-year follow-up in the population study of women in Gothenburg. BMC Womens Health. 2014;14:61.

87. Batty GD, Jokela M, Kivimaki M, Shipley M. Examining the Long-Term Association of Personality With Cause-Specific Mortality in London: Four Decades of Mortality Surveillance in the Original Whitehall Smoking Cessation Trial. Am J Epidemiol. 2016;184(6):436–41.

88. Shipley BA, Weiss A, Der G, Taylor MD, Deary IJ. Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: a 21-year prospective cohort study. Psychosom Med. 2007;69(9):923–31.

89. Coyne JC, Jaarsma T, Luttik M-L, van Sonderen E, van Veldhuisen DJ, Sanderman R. Lack of prognostic value of type D personality for mortality in a large sample of heart failure patients. Psychosom Med. 2011;73(7):557–62.

90. Šmigelskas K, Žemaitienė N, Julkunen J, Kauhanen J. Type A behavior pattern is not a predictor of premature mortality. Int J Behav Med. 2015;22(2):161–9.

91. Chida Y, Steptoe A. The Association of Anger and Hostility With Future Coronary Heart Disease: A Meta-Analytic Review of Prospective Evidence. J Am Coll Cardiol. 2009;53(11):936–46.

92. Hemingway H, Marmot M, Hemingway H. Psychsocial factors in the aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. BMJ. 1999;318(7196):1460–7.

93. Kawachi I, Sparrow D, Spiro A, Vokonas P, Weiss ST. A prospective study of anger and coronary heart disease. The Normative Aging Study. Circulation. 1996;94(9):2090–5.

94. Myrtek M. Meta-analyses of prospective studies on coronary heart disease, type A personality, and hostility. Int J Cardiol. 2001;79(2):245–51.

95. Lee HB, Offidani E, Ziegelstein RC, Bienvenu OJ, Samuels J, Eaton WW, et al. Five-Factor Model Personality Traits as Predictors of Incident Coronary Heart Disease in the Community: A 10.5-Year Cohort Study Based on the Baltimore Epidemiologic Catchment Area Follow-Up Study. Psychosomatics. 2014;55(4):352–61.

96. Jokela M, Pulkki-Råback L, Elovainio M, Kivimäki M. Personality traits as risk factors for stroke and coronary heart disease mortality: pooled analysis of three cohort studies. J Behav Med. 2014;37(5):881–9.

97. Haynes SG, Feinleib M, Kannel WB. The Relationship of Psychosocial Factors To Coronary Heart Disease in the Framingham Study. Am J Epidemiol. 1980;111(1):37–58.

98. Rosenman RH, Friedman M, Straus R, Jenkins CD, Zyzanski SJ, Wurm M. Coronary heart disease in the Western Collaborative Group Study. A follow-up experience of 4 and one-half years. J Chronic Dis. 1970;23(3):173–90.

99. Jenkins CD, Rosenman RH, Zyzanski SJ. Prediction of Clinical Coronary Heart Disease by a Test for the Coronary-Prone Behavior Pattern. N Engl J Med. 1974;290(23):1271–5.

100. Rosenman RH, Brand RJ, Sholtz RI, Friedman M. Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. Am J Cardiol. 1976;37(6):903–10.

101. Ikeda A, Iso H, Kawachi I, Inoue M, Tsugane S, JPHC Study Group. Type A behaviour and risk of coronary heart disease: the JPHC Study. Int J Epidemiol. 2008;37(6):1395–405.

102. Johnston DW, Cook DG, Shaper AG. Type A behaviour and ischaemic heart disease in middle aged British men. Br Med J (Clin Res Ed). 1987;295(6590):86–9.

103. Petticrew MP, Lee K, McKee M. Type A behavior pattern and coronary heart disease: Philip Morris's "crown jewel". Am J Public Health. 2012;102(11):2018–25.

104. Schwalbe FC. Relationship between Type A personality and coronary heart disease. Analysis of five cohort studies. J Fla Med Assoc. 1990;77(9):803–5.

105. Shekelle RB, Hulley SB, Neaton JD, Billings JH, Borhani NO, Gerace TA, et al. The MRFIT behavoir pattern study, II. Type A behavior and incidence of coronary heart disease. Am J Epidemiol. 1985;122(4):559–70.

106. Gallacher JEJ. Is Type A Behavior Really a Trigger for Coronary Heart Disease Events? Psychosom Med. 2003;65(3):339–46.

107. O'dell KR, Masters KS, Spielmans GI, Maisto SA. Does type-D personality predict outcomes among patients with cardiovascular disease? A meta-analytic review. J Psychosom Res. 2011;71:199–206.

108. Grande G, Romppel M, Barth J. Association Between Type D Personality and Prognosis in Patients with Cardiovascular Diseases: a Systematic Review and Meta-analysis. Ann Behav Med. 2012;43(3):299–310.

109. Larson NC, Barger SD, Sydeman SJ. Type D Personality is Not Associated with Coronary Heart Disease Risk in a North American Sample of Retirement-aged Adults. Int J Behav Med. 2012;20(2):277–85.

110. Jokela M, Batty GD, Hintsa T, Elovainio M, Hakulinen C, Kivimäki M. Is personality associated with cancer incidence and mortality? An individual-participant meta-analysis of 2156 incident cancer cases among 42,843 men and women. Br J Cancer. 2014;110(7):1820–4.

111. Nakaya N, Tsubono Y, Hosokawa T, Nishino Y, Ohkubo T, Hozawa A, et al. Personality and the Risk of Cancer. J Natl Cancer Inst. 2003;95(11):799–805.

112. Lemogne C, Consoli SM, Geoffroy-Perez B, Coeuret-Pellicer M, Nabi H, Melchior M, et al. Personality and the risk of cancer: a 16-year follow-up study of the GAZEL cohort. Psychosom Med. 2013;75(3):262–71.

113. Ranchor A V., Sanderman R, Coyne JC. Invited Commentary: Personality as a Causal Factor in Cancer Risk and Mortality--Time to Retire a Hypothesis? Am J Epidemiol. 2010;172(4):386–8.

114. Chapman BP, Fiscella K, Kawachi I, Duberstein PR. Personality, Socioeconomic Status, and All-Cause Mortality in the United States. Am J Epidemiol. 2010;171(1):83–92.

115. Allen MS, Magee CA, Vella SA, Laborde S. Bidirectional Associations Between Personality and Physical Activity in Adulthood. Health Psychol. 2017;36(4):332–6.

116. Allen MS, Vella SA, Laborde S. Sport participation, screen time, and personality trait development during childhood. Br J Dev Psychol. 2015;33(3):375–90.

117. Hakulinen C, Hintsanen M, Munafò MR, Virtanen M, Kivimäki M, Batty GD, et al. Personality and smoking: individual-participant meta-analysis of nine cohort studies. Addiction. 2015;110(11):1844–52.

118. Keller C, Siegrist M. Does personality influence eating styles and food choices? Direct and indirect effects. Appetite. 2015;84:128–38.

119. Lunn TE, Nowson CA, Worsley A, Torres SJ. Does personality affect dietary intake? Nutrition. 2014;30(4):403–9.

120. Murphy CM, Stojek MK, MacKillop J. Interrelationships among impulsive personality traits, food addiction, and Body Mass Index. Appetite. 2014;73:45–50.

Thesis Summary

The four papers presented in the following contribute to an enhanced understanding of the associations between lifestyle risk factors as well as personality and health outcomes. By building a lifestyle score based on the cancer prevention recommendations of the WCRF/AICR 2007, the importance of lifestyle patterns was investigated with respect to mortality. Furthermore, the lifestyle pattern of heavy smokers and obese, two populations already being at high risk for adverse health outcomes, was examined. The methodological issues arose how to deal with continuous outcome variables like BMI in the analysis. The novel approach of continuous logistic outcome regression was proposed to improve statistical analysis by using post hoc instead of ad hoc categorization of BMI. This has the two main advantages of preventing information loss and improving between study comparability. The association between BMI and smoking was used as a case study. Personality is another potential risk factor for NCD and we examined its association with mortality, focusing on type A personality. Additionally, possible interactions with lifestyle and sociodemographic factors were taken into account. In the following, the papers are summarized briefly and the contributions of the authors are declared.

Paper I

Adherence to the cancer prevention recommendations of the WCRF/AICR and mortality: a census-linked cohort

Tina Lohse, David Faeh, Matthias Bopp, Sabine Rohrmann for the Swiss National Cohort Study Group

The importance of single lifestyle factors like smoking and physical activity has been studied extensively and their preventive potential has been demonstrated. But in real life non-communicable diseases like cancer are developing under the presence of one or more risk factors. For lifestyle factors this corresponds to a lifestyle pattern, which is determining the risk of disease and mortality. In 2007, the WCRF and the AICR released common recommendations on cancer prevention. We built a lifestyle score including information on adherence to these recommendations with regard to BMI, physical activity, sedentary

behavior, energy density of food, as well as the consumption of fruits and vegetables, grains, processed meat, alcohol, and salt. We used data of the MONICA and NRP1A cohorts. By linking them with the SNC (census and death registry data) a mortality follow-up for up to 32 years was established. The lifestyle score was shown to be inversely associated with all-cause and total cancer mortality as well as mortality from lung, upper aerodigestive tract, stomach, and prostate cancer. Our results strengthened the relevance of adhering to these cancer prevention recommendations, which are addressing the lifestyle pattern rather than only single risk factors in order to reduce the burden of cancer.

TL and SR led the conceptualization and research methodology; TL wrote the first draft of the manuscript and conducted the statistical analysis. DF contributed his expertise during the process of manuscript preparation. All authors critically commented on the final version of the manuscript.

Paper II

Heavy Smoking Is More Strongly Associated with General Unhealthy Lifestyle than Obesity and Underweight

Tina Lohse, Sabine Rohrmann, Matthias Bopp, David Faeh

Heavy smokers and obese individuals are at high risk for non-communicable diseases. The presence of further unhealthy behaviors like physical inactivity and high alcohol intake further potentiates the risk. We looked at the lifestyle pattern of heavy smokers and obese individuals in order to investigate whether they were more likely to have an unhealthy lifestyle in general, compared to normal-weight never smokers. For this purpose, we used data of the Swiss Health Survey (1992-2012). Both heavy smokers and obese individuals were more likely to be physically inactive. Heavy smokers were additionally more likely to have high alcohol as well as low fruit and vegetable consumption. In heavy smokers the association was shown to be stronger, irrespectively of BMI category. Furthermore, we examined trends over time in prevalence and observed that the smoking prevalence decreased in normal-weight, but not in obese individuals. Preventive measures targeting heavy smokers or obese individuals should take into account the co-occurrence of lifestyle risk factors, especially in smokers.

TL, SR and DF led the conceptualization and research methodology; TL wrote the first draft of the manuscript and conducted the statistical analysis. MB contributed his expertise during the process of manuscript preparation. All authors critically commented on the final version of the manuscript.

Paper III

Continuous Outcome Logistic Regression for Analyzing Body Mass Index Distributions

Tina Lohse, Sabine Rohrmann, David Faeh, Torsten Hothorn

Categorizing continuous outcomes before statistical analysis (i.e. ad hoc categorization) leads to information loss. Moreover, the usage of different categorization schemes in epidemiological practice makes it difficult to ensure comparability across studies, especially in meta-analyses covering the existing evidence irrespective of categorization schemes. The novel approach of continuous outcome logistic regression was developed to improve statistical analyses of continuous outcomes, which previously had to be categorized for reasons of interpretability and communication of results. By performing the categorization after statistical analysis (i.e. post hoc categorization), this approach prevents information loss by allowing the estimation and analysis of the underlying continuous distribution. Furthermore, it has the advantage of improving between study comparability because it is independent of the available outcome data. The outcome data can be continuous or categorical or even a mix of both. In this paper, we empirically evaluate the approach by investigating Body Mass Index (BMI) distributions depending on smoking and gender based on the Swiss Health Survey 2012. It was obvious that more restrictive models, for example a conditional normal distribution with or without gender- and smoking specific variance, would describe the BMI distributions less accurately. The obtained model results were shown to be insensitive regarding BMI measurement scales or categorization schemes and to match previously reported knowledge about the impact of smoking and sex on BMI. Continuous outcome logistic regression was shown to be a sophisticated procedure to analyze continuous outcomes without the need of categorizing outcomes ad hoc for reasons of interpretability and communication of results.

TL and TH led the conceptualization and research methodology; TL and TH wrote the first draft of the manuscript; TH conducted the statistical analysis. DF and SR contributed their expertise during the process of manuscript preparation. All authors critically commented on the final version of the manuscript.

Paper IV

Type A personality and mortality: Competitiveness but not speed is associated with increased risk

Tina Lohse, Sabine Rohrmann, Aline Richard, Matthias Bopp, David Faeh for the Swiss National Cohort Study Group

The concept of type A behavior pattern (TABP) was developed in the context of cardiovascular disease and describes a personality, which is characterized by ambitiousness, competitiveness, easily aroused hostility, impatience and an exaggerated sense of time urgency. While previous studies showed no association with cancer, contradicting results were observed for cardiovascular outcomes. Different definitions and measurement instruments of TABP might be reasons for these contradicting results, as well as not taking into account the individual components of the measurement instrument applied. We used the data of the MONICA and the NRP1A cohorts linked with the SNC (37 years of follow-up) for the investigation of the association between mortality and the Bortner Scale, an instrument to measure TABP. For this, the subscale analysis approach proposed by Edwards et al. was applied. This approach implies that the Bortner Scale is additionally analyzed by its subscales competitiveness and speed. The total Bortner Scale was shown not to be associated with mortality. A positive association was observed in women on the subscale competitiveness for all-cause, CVD, and ischemic heart disease mortality. In men, an inverse association was shown for CVD mortality on the subscale speed. The observed associations were independent of lifestyle factors. The results of the full – lifestyle factor adjusted – model differed only marginally from those of the crude model. Testing for interactions between the Bortner Scale and lifestyle factors did also not show significant results. Future studies using the Bortner Scale should also perform a subscale analysis and allow thereby for strengthening the evidence that the subscales are associated with CVD mortality in an opposed manner. In individuals with high health awareness, sex specific preventive measures targeting competitiveness and speed might offer the potential for a reduction in mortality.

TL and DF led the conceptualization and research methodology; TL wrote the first draft of the manuscript and conducted the statistical analysis. DF, AR, and SR contributed their expertise during the process of manuscript preparation. All authors critically commented on the final version of the manuscript.

Annex

Paper I

Adherence to the cancer prevention recommendations of the WCRF/AICR and mortality: a census-linked cohort

Tina Lohse, David Faeh, Matthias Bopp, Sabine Rohrmann for the Swiss National Cohort Study Group.

Published in the American Journal of Clinical Nutrition. 2016;104(3):678–85.

The American Journal of Clinical Nutrition

Adherence to the cancer prevention recommendations of the World Cancer Research Fund/American Institute for Cancer Research and mortality: a census-linked cohort[1]

Tina Lohse,[2] David Faeh,[2,3] Matthias Bopp,[2] and Sabine Rohrmann[2] for the Swiss National Cohort Study Group*

[2]Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland; and [3]Health Division-Nutrition and Dietetics, Bern University of Applied Sciences, Bern, Switzerland

ABSTRACT

Background: Modifiable lifestyle factors linked to cancer offer great potential for prevention. Previous studies suggest an association between adherence to recommendations on healthy lifestyle and cancer mortality.

Objectives: The aim of this study was to examine whether adherence to the cancer prevention recommendations of the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) is associated with reduced all-cause, total cancer, and specific cancer type mortality.

Design: We built a lifestyle score that included 3 categories, based on the recommendations of the WCRF/AICR. Applying Cox regression models, we investigated the association with all-cause, total cancer, and specific cancer type mortality; in addition, we included cardiovascular disease (CVD) mortality. We used census- and death registry–linked survey data allowing a mortality follow-up for ≤32 y. Our analysis included 16,722 participants. Information on lifestyle score components and confounders was collected at baseline.

Results: Over a mean follow-up of 21.7 y, 3730 deaths were observed (1332 cancer deaths). Comparing best with poorest category of the lifestyle score showed an inverse association with all-cause (HR: 0.82; 95% CI: 0.75, 0.89) and total cancer (men only, HR: 0.69; 95% CI: 0.57, 0.84) mortality. We estimated that ∼13% of premature cancer deaths in men would have been preventable if lifestyle score levels had been high. Inverse associations were observed for lung, upper aerodigestive tract, stomach, and prostate cancer mortality [men and women combined, HR: 0.72; 95% CI: 0.51, 0.99; HR: 0.49; 95% CI: 0.26, 0.92; HR: 0.34; 95% CI: 0.14, 0.83; HR: 0.48; 95% CI: 0.28, 0.82 (men only), respectively]. CVD mortality was not associated with the lifestyle score (men and women combined, HR: 0.96; 95% CI: 0.82, 1.13).

Conclusions: Our results support the importance of adhering to recommendations for a healthy lifestyle with regard to all-cause and cancer mortality. To reduce the burden of cancer in the population, preventive measures should stress the potential of low-risk health behavior patterns rather than of specific risk factors only. *Am J Clin Nutr* 2016;104:678–85.

Keywords: WCRF/AICR recommendations, lifestyle, prevention, mortality, cancer

INTRODUCTION

Modifiable lifestyle factors play a major role in the development of noncommunicable diseases (1). For cancer prevention they offer a great potential to reduce the burden of disease and premature death on a population level (2–4). Smoking induces the greatest increase in mortality risk (5), but physical inactivity, unhealthy diet, high alcohol intake, and high BMI were also shown to be associated with increased risk of cancer and noncommunicable diseases in general (5–7). However, the concept of investigating risk factors individually does not capture their distribution in the population. Cancer has multiple lifestyle risk factors, and they are likely to occur coincidently (8–10). Furthermore, they were shown to act synergistically in the development of cancer (1, 7, 11, 12). Therefore, it is of interest to assess the influence of lifestyle in its entirety with health outcomes (13) to better understand the lifestyle health outcome association.

The World Cancer Research Fund (WCRF)[4] and the American Institute for Cancer Research (AICR) launched recommendations to avoid preventable cancer cases from unhealthy behaviors (14). Previous studies showed an association between adherence to these recommendations and total cancer, as well as specific cancer type, mortality (15–17).

Our aim was to investigate this association in 2 general population samples from Switzerland and to strengthen the existing evidence that lifestyle in its entirety, i.e., a lifestyle score, has an impact on the risk of preterm death. In our primary analysis, we aimed to examine whether adherence to the cancer

[1] Supported by the Swiss Cancer Research foundation (grant no. KFS-3048-08-2012). The Swiss Federal Statistical Office provided mortality and census data and support.

*To whom correspondence should be addressed. E-mail: tina.lohse@uzh.ch.

[4] Abbreviations used: ACS, American Cancer Society; AICR, American Institute for Cancer Research; CVD, cardiovascular disease; ICD, International Classification of Diseases; ISCED, International Standard Classification of Education; MONICA, MONItoring of trends and determinants in CArdiovascular disease; NRP1A, National Research Program 1A, a community-based prevention of cardiovascular disease; PAF, population-attributable fraction; RAP, rate advancement period; SNC, Swiss National Cohort; UADT, upper aerodigestive tract; WCRF, World Cancer Research Fund.

Received March 18, 2016. Accepted for publication June 23, 2016.
First published online August 3, 2016; doi: 10.3945/ajcn.116.135020.

prevention recommendations of the WCRF/AICR was associated with a reduced all-cause, total cancer, and specific cancer type mortality. In addition, we investigated its association with cardiovascular disease (CVD) mortality.

METHODS

Study design, setting, and participants

We used data from 2 population-based studies, the MONICA (MONItoring of trends and determinants in CArdiovascular disease) and the NRP1A (National Research Program 1A, a community-based primary prevention of CVD). The studies were linked with the SNC (Swiss National Cohort) to establish a mortality follow-up. The study participants were aged between 25 and 74 y at baseline.

As part of an international multicenter study initiated by the WHO, 3 waves of the MONICA study were conducted in Switzerland between 1983 and 1992 (18). The NRP1A study was conducted from 1977 to 1979 (19). Both studies included a health examination at baseline and a self-administered questionnaire. The vital status of participants and cause of death were followed up through the SNC (20, 21). The SNC is a national longitudinal research platform linking census records with federal death and migration records covering all residents of Switzerland. More details about the linkage process were given elsewhere (20). Finally, 97.0% of participants in the MONICA study and 93.8% of those in the NRP1A study were successfully linked with the SNC (21, 22). Approval for the SNC and the linkage with MONICA and NRP1A was obtained from the Ethics Committee of the Canton of Zurich (KEK-StV no. 13/06 and amendment of 12 June 2008).

Variables

We built a lifestyle score according to the recommendations of the WCRF/AICR, capturing available information from the MONICA and NRP1A cohorts (**Table 1**). Information for 7 of the 8 recommendations was available; only intake of dietary supplements was not assessed. The lifestyle score ranged from 0 to 9 points: physical activity, sedentary behavior, energy density, fruits/vegetables, grains, processed meat, alcohol, salt, and BMI category were all rated with 0 (nonadherence), 0.5 (partial adherence to the recommendation; not available for alcohol and grains) or 1 point (full adherence). Smoking status, education, nationality, marital status, language region, and study were considered as potential confounders.

Outcome

Causes of death were coded according to the International Classification of Diseases [ICD (8th revision until 1994, 10th revision since 1995)]. We investigated mortality from all causes, total cancer (ICD-8: 140–209, 225, and 230–239; ICD-10: C00–C97, D32–D33, and D37–D48), specific cancer type [lung (ICD-8: 162; ICD-10: C33–C34), colorectal (ICD-8: 153–154; ICD-10: C18–C21), upper aerodigestive tract (UADT; organs and tissues of the respiratory tract and upper part of the digestive tract, including the upper esophagus, but not the stomach, ICD-8: 140–150 and 161; ICD-10: C00–C15 and C32), lymphatic and hematopoietic tissue (abbreviated as "blood cancer" in the following—ICD-8: 200–209; ICD-10: C81–C86, C88, and C90–C96), pancreatic (ICD-8: 157; ICD-10: C25), urinary tract (ICD-8: 188–189; ICD-10: C67–C68), liver (ICD-8: 155; ICD-10: C22), stomach (ICD-8: 151; ICD-10: C16), breast (ICD-8: 174; ICD-10: C50), female genital tract (ICD-8: 180–184; ICD-10: C51–C58), and prostate (ICD-8: 185; ICD-10: C61)], and CVD (ICD-8: 410–458; ICD-10: I20–I99).

Data sources and assessment

Data on components of the lifestyle score and potential confounders were assessed by self-administered questionnaires (18, 19). Only height and weight, which were used to calculate BMI, were measured at baseline (23).

Statistical methods

We pooled data from the 3 MONICA waves and the NRP1A, because data collection on the variables of interest was comparable (Table 1); the categories of the lifestyle score components in particular were identical, except for sedentary behavior, energy density, and salt use. We decided that adding a study (including wave) variable to all models and stratifying for study (and wave) led to similar results. The lifestyle score was analyzed as categorical and continuous variable. Three categories were defined as follows to allow for a sufficient number of cases in each category: 0–3.5, 4–4.5, and 5–9 points. We used chained imputation for the independent variables (with a bootstrapping of 20) to increase the number of cases available for the Cox regression. Education (9.2%, $n = 1530$; NRP1A accounted for 98.1% of missing) and consumption of energy-dense foods (17.8%, $n = 2983$) as a score component contributed most to missing values (Table 1 and **Table 2**).

Cox regression was performed for all-cause, total cancer, specific cancer type, and CVD mortality. In addition, we determined a priori to stratify by sex for all-cause, total cancer, and CVD mortality. All Cox regression models were stratified by age (to prevent violation of the proportional hazards assumption) and adjusted for smoking status, education, nationality, marital status, language region, and study (MONICA wave 1–3; NRP1A). Smoking status was categorized into never, former, light (1–9 cigarettes/d), moderate (10–19 cigarettes/d), and heavy (>19 cigarettes/d). Education was included as highest degree obtained and categorized into mandatory [International Standard Classification of Education (ISCED) 1–2], secondary (ISCED 3–4), and tertiary (ISCED 5–8) (24). Nationality was included as being Swiss or foreign. Marital status was composed of 4 categories: single, married, widowed, and divorced or separated. Language region reflected cultural differences within Switzerland, and 4 categories were taken into account: German/Romansh, French, Italian, and German/French (bilingual region).

A trend test was used to examine whether the potential increase in risk for the outcome under investigation was linear. Multiplicative (likelihood ratio test) interaction was considered for sex and smoking. Additive interaction (Stata: add_int) was investigated in addition for smoking. We used the original data set to test for trend and interaction, because in Stata those methods are not implemented for imputed data (Stata: mi).

The relative importance of the score components was analyzed for those causes of death being statistically significant in the Cox regression models with the use of the imputed data set and the continuous score. For this purpose, one component was removed from the score, followed by our checking whether the reduced score was still significant.

Rate advancement periods (RAPs) were calculated for all-cause mortality only because of a lack of power for cause-specific

TABLE 1
Operationalization of the lifestyle score by study[1]

Score component	Recommendation	Operationalization	Category	Distribution, %
BMI	Maintain body weight within the normal range from age 21 y	MONICA and NRP1A: BMI (in kg/m^2): 18.5–24.9 = 1, 25–29.9 = 0.5, <18.5 or ≥30 = 0	0; 0.5; 1; missing	12.9; 35.9; 51.1; 0.1
Physical activity	Be moderately physically active, equivalent to brisk walking, for ≥30 min every day. As fitness improves, aim for ≥60 min of moderate or ≥30 min of vigorous physical activity every day	MONICA and NRP1A: ≥2 d/wk = 1, 1 d/wk = 0.5, <1 d/wk = 0	0; 0.5; 1; missing	55.7; 21.7; 20.6; 2.0
Sedentary behavior	Limit sedentary habits such as watching television	MONICA: Level of physical activity: mostly sitting = 0; walking, cycling, other regular activities such as gardening = 0.5; regular exercise = 1 NRP1A: Level of physical activity: sedentary (such as watching TV) = 0; average (such as walking, gymnastics, and badminton) = 0.5; exhausting (such as soccer, chopping wood, and digging) = 1	0; 0.5; 1; missing	30.6; 58.0; 9.7; 1.7
Energy density	Consume energy-dense foods sparingly	MONICA: Fat for cooking, bread, or salad (not butter or lard) = 1 + cut away fat from meat (always or often) = 1 + sweets yesterday (no) = 1* NRP1A: Fat for cooking, bread, or salad = 1 + cut away fat from meat (always or often) = 1+ chocolate yesterday (no) = 1*	0; 0.5; 1; missing	16.9; 34.5; 30.7; 17.8
Fruits and vegetables	Eat ≥5 portions or servings (≥400 g or 14 oz) of a variety of fruits and nonstarchy vegetables every day	MONICA and NRP1A: Yesterday: no fruits or vegetables = 0, either fruits or vegetables = 0.5, both fruits and vegetables = 1	0; 0.5; 1; missing	17.5; 48.1; 31.9; 2.6
Grains	Eat relatively unprocessed cereals (grains) and/or pulses (legumes) with every meal	MONICA and NRP1A: Yesterday: no = 0, yes = 1	0; 1; missing	54.0; 43.9; 2.1
Processed meat	For people who eat red meat, consume <500 g (18 oz) red meat/wk; very little if any as processed meat	MONICA and NRP1A: Yesterday: sausage products = 0; meat = 0.5; none = 1	0; 0.5; 1; missing	27.7; 53.8; 17.2; 1.3
Alcohol	If alcoholic drinks are consumed, limit consumption to ≤2 drinks/d for men and 1 drink/d for women	MONICA and NRP1A: Yesterday: yes = 0, no = 1	0; 1; missing	55.9; 43.4; 0.7
Salt	Avoid salt-preserved, salted, or salty foods; preserve foods without the use of salt	MONICA: Adding salt: always = 0, sometimes = 0.5, never = 1 NRP1A: Adding salt: always or often = 0, seldom or almost never 0.5, never = 1	0; 0.5; 1; missing	6.2; 43.5; 49.7; 0.5

[1]Only WCRF/AICR recommendations that could be operationalized are shown. *Energy-dense food: sum 0 = 0, 1 = 0.5, 2 or 3 = 1. AICR, American Institute for Cancer Research; MONICA, MONItoring of trends and determinants in CArdiovascular disease; NRP1A, National Research Program 1A, a community-based primary prevention of cardiovascular disease; WCRF, World Cancer Research Fund.

mortality. Based on an age dimension, the RAP estimates how much earlier death occurred in those being exposed than in those being unexposed (25). In addition, we estimated population-attributable fractions (PAFs) for all-cause and total cancer mortality. Both RAPs and PAFs were calculated with the use of the original data set and the categorical score.

We also performed sensitivity analyses to investigate reverse causation. For this purpose, the first 2 y of follow-up were excluded from the analysis. Another sensitivity analysis was performed to evaluate whether the results of the Cox regression were similar, when the original rather than the imputed data set (continuous or categorical score) was used. For the Cox regression models performed with the original data set, an additional category was created for confounding variables with missing values. All analyses were performed with the use of Stata 13.1; RAPs were calculated with the use of R statistical software version 3.2.3.

RESULTS

The study included 16,722 participants (8161 men and 8561 women) with a mean follow-up of 21.7 y (men, 20.9 y, and

TABLE 2
Characteristics of the study participants by lifestyle score categories and sex[1]

	Lifestyle score category				
	All	1	2	3	Imputed
Men	8161 (100.0)	2072 (25.4)	1842 (22.6)	2309 (28.3)	1938 (23.8)
Age, y	45.8 ± 12.0	46.3 ± 11.2	45.1 ± 11.7	44.1 ± 12.4	48.0 ± 12.1
Survival, y	20.9 ± 7.6	20.3 ± 7.4	21.4 ± 7.5	22.4 ± 7.7	19.4 ± 7.6
Smoking					
Never	2214 (27.1)	452 (21.8)	485 (26.3)	763 (33.0)	514 (26.5)
Former	2177 (26.7)	572 (27.6)	487 (26.4)	620 (26.9)	498 (25.7)
Light	884 (10.8)	191 (9.2)	206 (11.2)	285 (12.3)	202 (10.4)
Moderate	783 (9.6)	216 (10.4)	177 (9.6)	213 (9.2)	177 (9.1)
Heavy	1852 (22.7)	582 (28.1)	430 (23.3)	353 (15.3)	487 (25.1)
Imputed	251 (3.1)	59 (2.9)	57 (3.1)	75 (3.3)	60 (3.1)
Study					
MONICA I	1699 (20.8)	548 (26.5)	364 (19.8)	331 (14.3)	456 (23.5)
MONICA II	1750 (21.4)	592 (28.6)	421 (22.9)	461 (20.0)	276 (14.2)
MONICA III	1520 (18.6)	294 (14.2)	304 (16.5)	350 (15.2)	572 (29.5)
NRP1A	3192 (39.1)	638 (30.8)	753 (40.9)	1167 (50.5)	634 (32.7)
Education					
Mandatory	1982 (24.3)	607 (29.3)	424 (23.0)	356 (15.4)	595 (30.7)
Upper secondary	4027 (49.3)	1012 (48.8)	926 (50.3)	1192 (51.6)	897 (46.3)
Tertiary	1632 (20.0)	363 (17.5)	381 (20.7)	573 (24.8)	315 (16.3)
Imputed	520 (6.4)	90 (4.3)	111 (6.0)	188 (8.1)	131 (6.8)
Nationality					
Swiss	6363 (78.0)	1531 (73.9)	1445 (78.5)	1934 (83.8)	1453 (75.0)
Foreign	1796 (22.0)	539 (26.0)	397 (21.6)	375 (16.2)	485 (25.0)
Imputed	2 (0.0)	2 (0.1)	0 (0)	0 (0)	0 (0)
Women	8561 (100.0)	1345 (15.7)	1881 (22.0)	3710 (43.3)	1625 (19.0)
Age, y	46.3 ± 12.5	46.4 ± 11.9	46.2 ± 12.3	45.0 ± 12.3	49.7 ± 12.9
Survival, y	22.4 ± 7.0	21.3 ± 6.8	22.0 ± 6.7	23.2 ± 6.8	21.9 ± 7.7
Smoking					
Never	4884 (57.1)	695 (51.7)	1017 (54.1)	2140 (57.7)	1032 (63.5)
Former	1256 (14.7)	186 (13.8)	300 (16.0)	603 (16.3)	167 (10.3)
Light	545 (6.4)	94 (7.0)	108 (5.7)	247 (6.7)	96 (5.9)
Moderate	765 (8.9)	129 (10.0)	195 (10.4)	306 (8.3)	135 (8.3)
Heavy	795 (9.3)	186 (13.8)	197 (10.5)	275 (7.4)	137 (8.4)
Imputed	316 (3.7)	55 (4.1)	64 (3.4)	139 (3.8)	58 (3.6)
Study					
MONICA I	1625 (19.0)	372 (27.7)	407 (21.6)	581 (15.7)	265 (16.3)
MONICA II	1654 (19.3)	341 (25.4)	462 (24.6)	758 (20.4)	93 (5.7)
MONICA III	1605 (18.8)	238 (17.7)	344 (18.3)	616 (16.6)	407 (25.1)
NRP1A	3677 (43.0)	394 (29.3)	668 (35.5)	1755 (47.3)	860 (52.9)
Education					
Mandatory	3369 (39.4)	653 (48.6)	807 (42.9)	1165 (31.4)	744 (45.8)
Upper secondary	3223 (37.7)	483 (35.9)	701 (37.3)	1559 (42.0)	480 (29.5)
Tertiary	959 (11.2)	125 (9.3)	213 (11.3)	490 (13.2)	131 (8.1)
Imputed	1010 (11.8)	84 (6.3)	160 (8.5)	496 (13.4)	270 (16.6)
Nationality					
Swiss	7173 (83.8)	1061 (78.9)	1507 (80.1)	3268 (88.1)	1337 (82.3)
Foreign	1356 (15.8)	277 (20.6)	367 (19.5)	426 (11.5)	286 (17.6)
Imputed	32 (0.4)	7 (0.5)	7 (0.4)	16 (0.4)	2 (0.1)

[1]Values are means ± SDs or *n* (%). Missing information on score components and covariates were imputed for the Cox regression so that the whole sample could be included. For all other analyses, subjects with missing information could not be included. Data for marital status and language region are not shown. MONICA, MONItoring of trends and determinants in CArdiovascular disease; NRP1A, National Research Program 1A, a community-based primary prevention of cardiovascular disease.

women, 22.4 y) (Table 2). The mean age at baseline was 45.8 y in men and 46.3 y in women. Participants within the highest lifestyle score category, i.e., most adherent to a cancer-preventive lifestyle, were younger, more often never smoked and were Swiss nationals, less often were divorced or separated, and had a higher level of education. In addition, the proportion of participants with a high lifestyle score was greater in the NRP1A. Adherence to the recommendations was rather low for physical activity, sedentary behavior, and processed meat consumption (Table 1).

In total, 3730 deaths occurred, of which 1332 were caused by cancer and 1178 by CVD (**Table 3**). Lung (n = 259), blood (n = 145), and colorectal (n = 113) were the most common cancer-specific sites. Stomach (n = 39), urinary tract (n = 50), and liver (n = 51) were the rarest ones.

Both the categorical and the continuous lifestyle scores were inversely associated with all-cause and total cancer mortality, but not with CVD mortality (Table 3). Sex-stratified analyses of the categorical score showed that the association with all-cause mortality was stronger in men than in women (men, HR: 0.80; 95% CI: 0.71, 0.90; women, HR: 0.85; 95% CI: 0.73, 0.98, most compared with least adherent). In men, the risk of dying was even statistically significant when comparing low and moderate levels of the lifestyle score (HR: 0.87; 95% CI: 0.77, 0.98). The risk of dying from cancer (all sites) was inversely associated with the lifestyle score in men (HR: 0.69; 95% CI: 0.57, 0.84). Lung, UADT, stomach, and prostate cancer mortality also were inversely associated when comparing lowest and highest levels of the lifestyle score (HR: 0.72; 95% CI: 0.51, 0.99; HR: 0.49; 95% CI: 0.26, 0.92; HR: 0.34; 95% CI: 0.14, 0.83; HR: 0.48; 95% CI: 0.28, 0.82, respectively). Results were similar for the continuous score. We did not observe statistically significant interaction (neither additive nor multiplicative) of the lifestyle score with smoking, but we did observe significant interaction with sex for cancer mortality (multiplicative; P-interaction = 0.047 continuous and 0.616 categorical) and CVD mortality (multiplicative; P-interaction = 0.688 continuous and 0.036 categorical).

No statistically significant associations were observed when physical activity and sedentary behavior (all-cause mortality in women, and lung, and UADT cancer mortality) or BMI (all-cause mortality in women, and stomach, and prostate cancer mortality) were excluded from the score. Removing nutritional score components led to nonsignificant results with regard to lung and UADT cancer mortality (intake of fruits and vegetables, alcohol, and grains; salt in UADT only) (data not shown).

For the calculation of RAPs and PAFs, we used the original data set, which included 11,586 participants (5657 men and 5929 women). In men, additional gain of lifetime was greatest in those having low compared with moderate or high lifestyle score levels (1.15 y; 95% CI: 0.49, 1.81 y); high lifestyle scores did not add much (low and moderate compared with high, 1.17 y; 95% CI: 0.48, 1.88 y). In women, RAPs were not statistically significant (low compared with moderate and high, 0.84 y; 95% CI: −0.32, 1.99 y), and low and moderate compared with high, 0.65 y; 95% CI: −0.17, 1.46 y). We estimated that ∼6% (6.06%; 95% CI: 1.66%, 10.27%; in men, 8.03%; 95% CI: 1.28%, 14.32%) of premature deaths would have been preventable if all lifestyle score levels had been high. For total cancer mortality, the estimated PAF was even higher. Approximately 8% (7.93%; 95% CI: 0.34%, 14.96%; in men, 13.08%; 95% CI: 1.13%, 23.58%) of premature cancer deaths could have been prevented. In women, PAFs were not statistically significant (all-cause mortality, 4.17%; 95% CI: −1.21%, 9.27%; total cancer mortality, 3.81%; 95% CI: −5.79%, 12.54%). PAFs differed by cohort; the estimates were larger in the MONICA cohort (data not shown).

The sensitivity analysis on reverse causation, i.e., exclusion of the first 2 y of follow-up, showed changing results for CVD mortality from no association to a significant association (continuous score, men and women combined, 0.94; 95% CI: 0.89, 0.99), but no change in the results for all-cause or total cancer mortality. Results of the Cox regression were consistent for all-cause, total cancer, lung cancer, prostate cancer, and CVD mortality: use of the imputed or the original data set did not change the results appreciably. UADT and stomach cancer mortality results were comparable in the imputed data set for the categorical and the continuous lifestyle scores. But for the original data set, no significant associations were observed, which most likely was because of the small number of UADT and stomach cancer deaths.

DISCUSSION

Adherence to the recommendations of the WCRF/AICR was associated with reduced all-cause and total cancer mortality, as well as lung, UADT, stomach, and prostate cancer mortality. However, the association with cancer mortality was statistically significant in men only.

Our results strengthen the existing evidence that adherence to a healthy lifestyle is associated with all-cause and total cancer mortality (15–17). Others showed the relevance of a general healthy lifestyle to prevent cancer and reduce all-cause mortality by building a lifestyle score based on the recommendations of the AICR only (26) or the American Cancer Society (ACS) (27–29). However, in our study, the association was considerably weaker for women than for men. We assume that this was due to an overall healthier behavior in women.

In line with our results, Romaguera et al. (16) observed significant associations of the WCRF/AICR score with stomach, lung, and UADT cancer, but not with prostate cancer. Although our estimates were larger, the greatest association was also shown for stomach cancer, followed by UADT and lung cancers. Romaguera et al. (16) showed a relation of the lifestyle score with colon, breast, endometrial, kidney, liver, and esophagus cancers, which we did not see in our study. Kabat et al. (29) used the recommendations of the ACS to build a score of adherence, and showed significant associations for 16 cancer-specific sites. The strongest associations were observed for gallbladder, endometrial, liver, and colon cancer. Several studies investigated whether specific cancer types were associated with the WCRF/AICR recommendations on lifestyle. Most studies focused on breast cancer (30–34), but also colorectal (35) and pancreatic (36) cancer risk were investigated. Results of these studies showed consistently that cancer incidence was reduced if adherence to the WCRF/AICR recommendations was high (30, 32–36); only Fanidi et al. (31) did not observe an association between breast cancer risk and adherence to the WCRF/AICR recommendations. In our analysis, we did not observe an association of the WCRF/AICR score with the risk of dying from colorectal cancer. This is in contrast to several previous studies and might be due to a small number of cases.

Similar to us, Cerhan et al. (26) did not observe an association of adherence to the AICR recommendations with CVD mortality in a female population. But in our sensitivity analysis, the exclusion of the first 2 y of follow-up yielded a significant association of the lifestyle score with CVD mortality. This may indicate reverse causation, i.e., participants might have changed their lifestyle after having been diagnosed with, e.g., hypertension or myocardial infarction. McCullough et al. (27) and Vergnaud et al. (17) observed an association with CVD mortality when applying the ACS and the WCRF/AICR recommendations, respectively.

TABLE 3
HRs (95% CIs) for the association between the lifestyle score and all-cause, total cancer, specific cancer type, and CVD mortality[1]

	Lifestyle score						
	Categorical					Continuous	
Mortality	1[2]	2	3	Missing	*P*-trend[3]		*P*-trend[3]
All-cause							
Overall	1	0.87 (0.79, 0.95)	0.82 (0.75, 0.89)		0.004	0.93 (0.90, 0.95)	0.001
Cases, *n*	766	759	1190	1015			
Men	1	0.87 (0.77, 0.98)	0.80 (0.71, 0.90)		0.075	0.91 (0.88, 0.95)	0.012
Cases, *n*	534	442	541	569			
Women	1	0.90 (0.76, 1.05)	0.85 (0.73, 0.98)		0.681	0.94 (0.91, 0.99)	0.475
Cases, *n*	232	317	649	446			
Interaction for sex					0.374		0.065
Cancer							
Overall	1	0.83 (0.72, 0.97)	0.74 (0.64, 0.86)		0.001	0.90 (0.86, 0.94)	0.001
Cases, *n*	300	284	408	340			
Men	1	0.80 (0.66, 0.97)	0.69 (0.57, 0.84)		0.001	0.87 (0.81, 0.93)	0.001
Cases, *n*	211	158	172	212			
Women	1	0.91 (0.70, 1.17)	0.80 (0.64, 1.01)		0.645	0.94 (0.88, 1.01)	0.672
Cases, *n*	89	126	236	128			
Interaction for sex					0.616		0.047
Specific cancer types							
Lung	1	0.93 (0.68, 1.28)	0.72 (0.51, 0.99)		0.001	0.90 (0.81, 1.00)	0.001
Cases, *n*	71	61	55	72			
UADT	1	0 0.82 (0.47, 1.45)	0.49 (0.26, 0.92)		0.002	0.82 (0.67, 1.00)	0.003
Cases, *n*	23	19	15	18			
Stomach	1	0.60 (0.25, 1.39)	0.34 (0.14, 0.83)		0.021	0.71 (0.54, 0.95)	0.028
Cases, *n*	11	4	6	18			
Colorectal	1	1.15 (0.68, 1.96)	0.84 (0.50, 1.42)		0.912	0.86 (0.73, 1.02)	0.653
Cases, *n*	18	26	35	34			
Liver	1	0.56 (0.25, 1.26)	1.07 (0.54, 2.11)		0.909	0.98 (0.77, 1.24)	0.633
Cases, *n*	12	8	20	11			
Pancreatic	1	0.83 (0.43, 1.60)	0.65 (0.35, 1.20)		0.754	0.88 (0.72, 1.07)	0.804
Cases, *n*	15	16	24	17			
Urinary tract	1	0.38 (0.15, 0.97)	0.63 (0.31, 1.28)		0.835	0.99 (0.78, 1.26)	0.747
Cases, *n*	13	7	19	11			
Blood	1	1.24 (0.76, 2.02)	1.04 (0.65, 1.67)		0.124	0.98 (0.85, 1.13)	0.070
Cases, *n*	21	36	58	30			
Prostate	1	0.67 (0.39, 1.18)	0.48 (0.28, 0.82)		0.053	0.79 (0.66, 0.95)	0.092
Cases, *n*	32	18	21	27			
Breast	1	0.67 (0.36, 1.24)	0.76 (0.45, 1.30)		0.439	0.91 (0.77, 1.08)	0.265
Cases, *n*	18	18	37	25			
FGT	1	0.82 (0.40, 1.65)	0.66 (0.35, 1.25)		0.799	0.90 (0.73,1.09)	0.646
Cases, *n*	11	16	33	14			
CVD							
Overall	1	0.92 (0.77, 1.09)	0.96 (0.82, 1.13)		0.203	0.97 (0.92,1.02)	0.539
Cases, *n*	208	226	394	350			
Men	1	0.91 (0.72, 1.13)	0.97 (0.79, 1.18)		0.087	0.99 (0.92,1.06)	0.177
Cases, *n*	148	135	194	188			
Women	1	0.94 (0.69, 1.28)	0.97 (0.74, 1.28)		0.312	0.95 (0.88,1.03)	0.820
Cases, *n*	60	91	200	162			
Interaction for sex					0.036		0.688

[1]Cox regression with the use of the imputed data set; models were adjusted for education, marital status, study, language region, nationality, and smoking status. CVD, cardiovascular disease; FGT, female genital tract; UADT, upper aerodigestive tract.
[2]Reference category.
[3]*P*-trend test for linearity and likelihood ratio test for multiplicative interaction, with the use of the original data set.

Similar to others, we observed that removing one component of the lifestyle score did not appreciably change the association observed for total cancer mortality (men and women combined) (17), but the relative importance of individual score components differed with respect to their relevance for specific cancer types (16). For example, for lung and UADT cancer mortality, physical activity, sedentary behavior, and nutrition seemed to be of greater importance than the other lifestyle score components.

We observed statistically significant RAPs for all-cause mortality in men, but not in women. The estimate of ∼1.2 y was similar to what was found by others; however, their estimation was for both men and women combined (17). For fruit and vegetable consumption, the estimated RAP was comparable with the 1.12 y observed in the European Prospective Investigation into Cancer and Nutrition (37). In relation to smoking, these estimates for all-cause mortality were smaller. The Chances Consortium observed RAPs of 6.4 y for current smokers and 2.4 y for former smokers compared with never smokers (38). In the third NHANES, the RAP for the combination of 4 lifestyle factors (all compared with none: never smoking, healthy diet, adequate physical activity, and moderate alcohol consumption) was estimated to be 11.1 y for all-cause mortality (39).

Approximately 25% of cancer deaths in Western countries were estimated to be preventable by adherence to common recommendations on diet, nutrition, physical activity, and body fatness (40). Our estimate of 8% was much lower than that. But others also observed a lower estimate of ∼12%, and, as they already discussed (16), this might be due to the fact that our study population was healthier than the general population (41) and that the prevalence of adherence to the recommendations was considerably greater in the NRP1A cohort.

Our study had strengths and limitations. The whole range of the lifestyle score was represented in our study, and participants were followed for up to 32 y, with low loss to follow-up. The exposure was assessed only once at baseline by self-report, which might have biased the results toward the null. A person's lifestyle is rather stable over the life course, but individuals tend to overreport or overestimate presumed healthy behaviors. This might be especially true for the NRP1A, designed as a primary prevention intervention in which participants were educated on behaviors defined as healthy and therefore might have even more strongly overreported or overestimated healthy behaviors. Our analysis included all components of the WCRF/AICR recommendations, except for the intake of dietary supplements. The assessment of the lifestyle score components was similar for the 2 cohorts pooled, and the bias introduced by pooling is expected to be minor. The available data on dietary intake was limited, given that only the 24-h recall has been assessed. In a previous analysis, we showed that including the variables on "was yesterday a weekday" and "was yesterday a normal or an unusual day regarding your diet" did not affect the association (42). Equal weights were given to the risk factors included in the lifestyle score and an overall estimate was calculated, not taking into account differences between specific cancer types. Furthermore, it has to be taken into account that we investigated the association of adherence to the WCRF/AICR recommendations with mortality only and not with incident cases. By performing data imputation, we were able to present more precise estimates of the association under investigation without changing the association, as shown by the sensitivity analysis. Nevertheless, the number of cases was relatively low for some cancer-specific–type mortalities, especially stomach, urinary tract, and liver cancers; therefore, the results have to be interpreted with caution. Concerning generalizability, we assume that the results of our analysis tend to underestimate the real association between mortality and healthy lifestyle.

In conclusion, our results support the importance of a general healthy lifestyle with regard to all-cause and cancer mortality. To reduce the burden of cancer in the population, preventive measures should stress the potential of low-risk health behavior and communicate the diverse opportunities for improvement, rather than focusing on specific risk factors only. To deepen our understanding of the association between cancer and lifestyle, future research should consider a life course approach.

We thank the members of the Swiss National Cohort Study Group: Matthias Egger (Chairman of the Executive Board), Adrian Spoerri, and Marcel Zwahlen (all Bern); Milo Puhan (Chairman of the Scientific Board) and Matthias Bopp (both Zurich); Nino Künzli (Basel); Fred Paccaud (Lausanne); and Michel Oris (Geneva).

The authors' responsibilities were as follows—TL and SR: led the conceptualization and research methodology; TL: wrote the first draft of the manuscript and conducted the statistical analysis; and all authors: revised the final draft of the manuscript critically and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women. Arch Intern Med 2010;170:711–18.
2. Danaei G, Vander Hoorn S, Lopez AD, Murray CJL, Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet 2005;366:1784–93.
3. Dartois L, Fagherazzi G, Boutron-Ruault M-C, Mesrine S, Clavel-Chapelon F. Association between five lifestyle habits and cancer risk: results from the E3N cohort. Cancer Prev Res (Phila) 2014;7:516–25.
4. Schottenfeld D, Beebe-Dimmer JL. Buffler PA, Omenn GS. Current perspective on the global and United States cancer burden attributable to lifestyle and environmental risk factors. Annu Rev Public Health 2013;34:97–117.
5. Behrens G, Fischer B, Kohler S, Park Y, Hollenbeck AR, Leitzmann MF. Healthy lifestyle behaviors and decreased risk of mortality in a large prospective study of U.S. women and men. Eur J Epidemiol 2013;28:361–72.
6. Ford ES, Bergmann MM, Boeing H, Li C, Capewell S. Healthy lifestyle behaviors and all-cause mortality among adults in the United States. Prev Med 2012;55:23–7.
7. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. BMJ 2008;337:a1440.
8. Hausdorf K, Eakin E, Whiteman D, Rogers C, Aitken J, Newman B. Prevalence and correlates of multiple cancer risk behaviors in an Australian population-based survey: results from the Queensland Cancer Risk Study. Cancer Causes Control 2008;19:1339–47.
9. Schuit AJ, van Loon AJM, Tijhuis M, Ocké MC. Clustering of lifestyle risk factors in a general adult population. Prev Med 2002;35:219–24.
10. Pronk NP, Anderson LH, Crain AL, Martinson BC, O'Connor PJ, Sherwood NE, Whitebird RR. Meeting recommendations for multiple healthy lifestyle factors. Prevalence, clustering, and predictors among adolescent, adult, and senior health plan members. Am J Prev Med 2004;27(2 Suppl):25–33.
11. Petersen KEN, Johnsen NF, Olsen A, Albieri V, Olsen LKH, Dragsted LO, Overvad K, Tjønneland A, Egeberg R. The combined impact of adherence to five lifestyle factors on all-cause, cancer and cardiovascular mortality: a prospective cohort study among Danish men and women. Br J Nutr 2015;113:849–58.

12. Lee C-D, Sui X, Hooker SP, Hébert JR, Blair SN. Combined impact of lifestyle factors on cancer mortality in men. Ann Epidemiol 2011;21:749–54.
13. Martin-Diener E, Meyer J, Braun J, Tarnutzer S, Faeh D, Rohrmann S, Martin BW. The combined effect on survival of four main behavioural risk factors for non-communicable diseases. Prev Med 2014;65:148–52.
14. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC): AICR; 2007.
15. Hastert TA, Beresford SAA, Sheppard L, White E. Adherence to the WCRF/AICR cancer prevention recommendations and cancer-specific mortality: results from the Vitamins and Lifestyle (VITAL) Study. Cancer Causes Control 2014;25:541–52.
16. Romaguera D, Vergnaud A-C, Peeters PH, van Gils CH, Chan DSM, Ferrari P, Romieu I, Jenab M, Slimani N, Clavel-Chapelon F, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012;96:150–63.
17. Vergnaud A-C, Romaguera D, Peeters PH, van Gils CH, Chan DSM, Romieu I, Freisling H, Ferrari P, Clavel-Chapelon F, Fagherazzi G, et al. Adherence to the World Cancer Research Fund/American Institute for Cancer Research guidelines and risk of death in Europe: results from the European Prospective Investigation into Nutrition and Cancer cohort study. Am J Clin Nutr 2013;97:1107–20.
18. Böthig S. WHO MONICA Project: objectives and design. Int J Epidemiol 1989;18:S29–S37.
19. Gutzwiller F, Nater B, Martin J. Community-based primary prevention of cardiovascular disease in Switzerland: methods and results of the National Research Program (NRP 1A). Prev Med 1985;14:482–91.
20. Bopp M, Spoerri A, Zwahlen M, Gutzwiller F, Paccaud F, Braun-Fahrländer C, Rougemont A, Egger M. Cohort profile: the Swiss National Cohort—a longitudinal study of 6.8 million people. Int J Epidemiol 2009;38:379–84.
21. Bopp M, Braun J, Faeh D, Gutzwiller F. Establishing a follow-up of the Swiss MONICA participants (1984-1993): record linkage with census and mortality data. BMC Public Health 2010;10:562.
22. Bopp M, Braun J, Gutzwiller F, Faeh D. Health risk or resource? Gradual and independent association between self-rated health and mortality persists over 30 years. PLoS One 2012;7:e30795.
23. Faeh D, Marques-Vidal P, Chiolero A, Bopp M. Obesity in Switzerland: do estimates depend on how body mass index has been assessed? Swiss Med Wkly 2008;138:204–10.
24. UNESCO Institute for Statistics. International Standard Classification of Education—ISCED 2011. Montreal (Canada): UNESCO Institute for Statistics; 2012.
25. Brenner H, Gefeller O, Greenland S. Risk and rate advancement periods as measures of exposure impact on the occurrence of chronic diseases. Epidemiology 1993;4:229–36.
26. Cerhan JR, Potter JD, Gilmore JME, Janney CA, Kushi LH, Lazovich D, Anderson KE, Sellers TA, Folsom AR. Adherence to the AICR cancer prevention recommendations and subsequent morbidity and mortality in the Iowa Women's Health Study cohort. Cancer Epidemiol Biomarkers Prev 2004;13:1114–20.
27. McCullough ML, Patel AV, Kushi LH, Patel R, Willett WC, Doyle C, Thun MJ, Gapstur SM. Following cancer prevention guidelines reduces risk of cancer, cardiovascular disease, and all-cause mortality. Cancer Epidemiol Biomarkers Prev 2011;20:1089–97.
28. Thomson CA, McCullough ML, Wertheim BC, Chlebowski RT, Martinez ME, Stefanick ML, Rohan TE, Manson JE, Tindle HA, Ockene J, et al. Nutrition and physical activity cancer prevention guidelines, cancer risk, and mortality in the women's health initiative. Cancer Prev Res (Phila) 2014;7:42–53.
29. Kabat GC, Matthews CE, Kamensky V, Hollenbeck AR, Rohan TE. Adherence to cancer prevention guidelines and cancer incidence, cancer mortality, and total mortality: a prospective cohort study. Am J Clin Nutr 2015;101:558–69.
30. Catsburg C, Miller AB, Rohan TE. Adherence to cancer prevention guidelines and risk of breast cancer. Int J Cancer 2014;135:2444–52.
31. Fanidi A, Ferrari P, Biessy C, Ortega C, Angeles-Llerenas A, Torres-Mejia G, Romieu I. Adherence to the World Cancer Research Fund/American Institute for Cancer Research cancer prevention recommendations and breast cancer risk in the Cancer de Màma (CAMA) study. Public Health Nutr 2015; 18:3337–48.
32. Hastert TA, Beresford SAA, Patterson RE, Kristal AR, White E. Adherence to WCRF/AICR cancer prevention recommendations and risk of postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev 2013;22:1498–508.
33. Nomura SJO, Inoue-Choi M, Lazovich D, Robien K. WCRF/AICR recommendation adherence and breast cancer incidence among postmenopausal women with and without non-modifiable risk factors. Int J Cancer 2016;138:2602–15.
34. Harris HR, Bergkvist L, Wolk A. Adherence to the World Cancer Research Fund/American Institute for Cancer Research recommendations and breast cancer risk. Int J Cancer 2016;138:2657–64.
35. Kirkegaard H, Johnsen NF, Christensen J, Frederiksen K, Overvad K, Tjønneland A. Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. BMJ 2010;341:c5504.
36. Lucas AL, Bravi F, Boffetta P, Polesel J, Serraino D, La Vecchia C, Bosetti C. Adherence to World Cancer Research Fund/American Institute for Cancer Research recommendations and pancreatic cancer risk. Cancer Epidemiol 2016;40:15–21.
37. Leenders M, Sluijs I, Ros MM, Boshuizen HC, Siersema PD, Ferrari P, Weikert C, Tjonneland A, Olsen A, Boutron-Ruault MC, et al. Fruit and vegetable consumption and mortality: European Prospective Investigation Into Cancer and Nutrition. Am J Epidemiol 2013;178:590–602.
38. Müezzinler A, Mons U, Gellert C, Schöttker B, Jansen E, Kee F, O'Doherty MG, Kuulasmaa K, Freedman ND, Abnet CC, et al. Smoking and all-cause mortality in older adults: results from the CHANCES consortium. Am J Prev Med 2015;49:e53–63.
39. Ford ES, Zhao G, Tsai J, Li C. Low-risk lifestyle behaviors and all-cause mortality: findings from the National Health and Nutrition Examination Survey III Mortality Study. Am J Public Health 2011;101:1922–9.
40. World Cancer Research Fund, American Institute for Cancer Research. Policy and action for cancer prevention—food, nutrition, and physical activity: a global perspective. Washington (DC): AICR; 2009.
41. Bopp M, Braun J, Faeh D. Variation in mortality patterns among the general population, study participants, and different types of non-participants: Evidence from 25 years of follow-up. Am J Epidemiol 2014;180:1028–35.
42. Vormund K, Braun J, Rohrmann S, Bopp M, Ballmer P, Faeh D. Mediterranean diet and mortality in Switzerland: an alpine paradox? Eur J Nutr 2015;54:139–48.

The American Journal of Clinical Nutrition

Paper II

Heavy Smoking Is More Strongly Associated with General Unhealthy Lifestyle than Obesity and Underweight

Tina Lohse, Sabine Rohrmann, Matthias Bopp, David Faeh

Published in PLoS ONE. 2016;11(2):1–13.

PLOS ONE

RESEARCH ARTICLE

Heavy Smoking Is More Strongly Associated with General Unhealthy Lifestyle than Obesity and Underweight

Tina Lohse*, Sabine Rohrmann, Matthias Bopp, David Faeh

Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich, Zurich, Switzerland

* tina.lohse@uzh.ch

OPEN ACCESS

Citation: Lohse T, Rohrmann S, Bopp M, Faeh D (2016) Heavy Smoking Is More Strongly Associated with General Unhealthy Lifestyle than Obesity and Underweight. PLoS ONE 11(2): e0148563. doi:10.1371/journal.pone.0148563

Editor: Salomon Amar, Boston University, UNITED STATES

Received: April 17, 2015

Accepted: January 19, 2016

Published: February 24, 2016

Data Availability Statement: Individual data of the Swiss Health Survey are property of the Swiss Federal Statistical Office (SFSO) and may only be made available by SFSO. Requests for access have to be submitted to Mr. Marco D'Angelo (head of division, MarcoDAngelo@bfs.admin.ch). For information contact sgb12@bfs.admin.ch.

Funding: This work was supported by the Swiss Cancer Research foundation (SCR), grant no. KFS-3048-08-2012, http://www.krebsliga.ch, and the Swiss Federal Statistical Office. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background

Smoking and obesity are major causes of non-communicable diseases. We investigated the associations of heavy smoking, obesity, and underweight with general lifestyle to infer which of these risk groups has the most unfavourable lifestyle.

Methods

We used data from the population-based cross-sectional Swiss Health Survey (5 rounds 1992–2012), comprising 85,575 individuals aged≥18 years. Height, weight, smoking, diet, alcohol intake and physical activity were self-reported. Multinomial logistic regression was performed to analyse differences in lifestyle between the combinations of body mass index (BMI) category and smoking status.

Results

Compared to normal-weight never smokers (reference), individuals who were normal-weight, obese, or underweight and smoked heavily at the same time had a poorer general lifestyle. The lifestyle of obese and underweight never smokers differed less from reference. Regardless of BMI category, in heavy smoking men and women the fruit and vegetable consumption was lower (e.g. obese heavy smoking men: relative risk ratio (RRR) 1.69 [95% confidence interval 1.30;2.21]) and high alcohol intake was more common (e.g. normal-weight heavy smoking women 5.51 [3.71;8.20]). In both sexes, physical inactivity was observed more often in heavy smokers and obese or underweight (e.g. underweight never smoking 1.29 [1.08;1.54] and heavy smoking women 2.02 [1.33;3.08]). A decrease of smoking prevalence was observed over time in normal-weight, but not in obese individuals.

Conclusions

Unhealthy general lifestyle was associated with both heavy smoking and BMI extremes, but we observed a stronger association for heavy smoking. Future smoking prevention

Competing Interests: The authors have declared that no competing interests exist.

measures should pay attention to improvement of general lifestyle and co-occurrence with obesity and underweight.

Introduction

Smoking and obesity are the most important modifiable risk factors of non-communicable diseases (NCD) [1–3]. Evidence is less clear for underweight [4,5]. However, similarly to obese individuals and smokers, it was shown that underweight individuals have an increased risk of premature death [6,7]. Investigations of the health impact of extreme body mass index (BMI) combined with smoking found that obese and underweight current smokers had the highest overall, cancer and cardiovascular disease mortality risk [8]. Non-smoking and maintaining healthy BMI, but also related risk factors such as healthy diet, low to moderate alcohol intake and physical activity offer substantial potential for the reduction of premature death and NCD burden in the population [9,10].

Unfavourable lifestyle factors are likely to occur coincidentally. Studies on how lifestyle factors are related and cluster revealed that smoking and educational level are driving factors, unfortunately they did not take BMI into account [11–13]. In affluent countries like Switzerland, obesity gained relevance as its prevalence was increased over the past decades, whereas the prevalence of smoking decreased in the general population [14,15]. However, it remains unknown whether this decrease occurred also in those most at risk (i.e. obese individuals) or mainly in healthier and health conscious people. Therefore we aimed to investigate the general lifestyle of obese individuals, heavy smokers, and obese heavy smokers to get a better understanding of the distribution of lifestyle risk factors. These populations are already at high risk of NCD and the coincidence with further unhealthy lifestyles would worsen their risk profile. We also included underweight in our analysis to contribute to the discussion on whether the increased mortality risk of underweight individuals is explained by associated lifestyle factors [6,16].

It was our first objective to compare the role of obesity, underweight and heavy smoking regarding the tendency of clustering with other NCD relevant lifestyle factors and with sociodemographic factors. Secondly, we aimed at investigating the temporal changes in the prevalence of the combination of obesity and underweight respectively with heavy smoking.

Methods

Population and data collection

The Swiss Health Survey (SHS) is a population-based cross-sectional survey conducted every 5 years since 1992 by the Swiss Federal Statistical Office [17]. Study samples were obtained by stratified random sampling out of a database containing all private household landline telephone numbers. This database was built with linkage of data from resident registries and telephone companies. Since 2012, an additional recruitment option was implemented. For those subjects who were randomly selected through resident registries and had no landline telephone number available, a letter was sent out to obtain contact information (landline or mobile telephone number) by prepaid answer postcard. Data was collected with telephone interview and self-administered questionnaire, additionally. The participation rate ranged from 71% in 1992 to 54% in 2012. For this study, we restricted the sample to individuals aged≥18 years.

The data collection and data storage for the SHS does not require formal approval by an ethical committee. This data collection is specifically permitted under Swiss law (Verordnung

über die Durchführung von statistischen Erhebungen des Bundes vom 30. Juni 1993 (SR 431.012.1) and Verordnung über die eidgenössische Volkszählung vom 19. Dezember 2008 (SR 431.112.1)). Individuals invited to participate received a brief description of the study and could decline to participate or withdraw at any time. Participants' responses were treated confidentially and aggregated anonymous responses were utilized for analyses presented herein.

Outcome

Height, weight, and smoking status were self-reported by telephone interview (see S1 Table). BMI was calculated as weight in kilograms divided by the square of height in metres. We categorized BMI (kg/m^2) into underweight <18.5, normal-weight ≥18.5–<25, overweight ≥25–<30, and obesity ≥30 [18]; smoking status into never, former, light (1–9 cigarettes per day), moderate (10–19), and heavy smokers (>19). Never smokers stated that they did not currently smoke and never regularly smoked during more than six months; former smokers reported not smoking currently but having smoked for more than 6 months during their life course. One cigarillo or pipe was counted as 2 cigarettes and 1 cigar as 4 cigarettes. The outcome variable had 20 categories, composed of the combination of BMI category and smoking status.

Exposure and Covariates

We selected three lifestyle proxies in order to explore the general health behaviour. These were assessed by telephone interview and self-administered questionnaire: fruit and vegetable consumption, physical activity, and alcohol intake. In Switzerland, fruit and vegetable consumption—as healthy diet proxy—was associated with lower mortality, also in combination with other NCD factors [10]. For all 5 rounds of the SHS information on the number of days per week fruits and vegetables were consumed was available. We chose to categorize as closest to the "5-a-day" recommendation as possible [19]. Because of the inconsistency of the collected information across surveys, we had to choose a fairly crude categorisation. Fruit and vegetable consumption was combined in one binary variable that comprised the information on whether both fruits and vegetables were consumed daily or not. We previously showed the importance of leisure-time physical activity in avoiding premature death [20]; hence we included weekly leisure-time physical activity in the analysis. The variable was defined as the number of days per week a subject started to sweat during leisure time physical activity and was categorized as >2 days, 1–2 days, and none. Alcohol intake was categorized into low, moderate, and high based on its sex specific risk for adverse health consequences. For men, the cut-offs were <40 to <60g of alcohol per day, for women <20 to <40g. For 4,500 participants of the SHS 1992, information on alcohol intake was only available from the telephone interview. Because this information was not comparable to that obtained from the questionnaire, we added a missing category to the alcohol variable. Education was included as highest degree obtained and was categorized into mandatory (International Standard Classification of Education, ISCED 1–2), secondary II (ISCED 3–4), and tertiary (ISCED 5–8) [21].

Statistical analysis

We pooled the data of the five SHS and included a survey variable in the model. All analyses were weighted to the general population of Switzerland [17] and stratified by sex. We stratified for sex because of existing evidence for variations between sexes which also were obvious in our data. Differences in prevalence of smoking status and BMI categories were substantial between men and women as well as in the distribution of the exposures (fruit and vegetables, physical activity, and alcohol intake). Furthermore, it is known that the reasons for smoking vary by sex and this may lead to differences in their association with further lifestyle factors

[22,23]. We performed multinomial logistic regression (STATA command: mlogit) in order to examine whether heavy smoker, obese or underweight individuals as well as obese and underweight heavy smokers were prone to have additional unhealthy lifestyle factors, compared to normal-weight never smokers. Multinomial regression was used to investigate associations between a categorical outcome with more than 2 categories and the exposure. The outcome was defined as a categorical variable obtained by the combination of BMI category with smoking status category. All smoking-BMI-category-combinations (4x5) were included in the analyses. However, for this study, we focussed on the results for heavy smoking and BMI extremes (underweight and obesity) and their presentation. The three lifestyle variables were included in the model, as well as educational level, nationality, language region, survey (categorisation, see Tables 1 and 2), and age. We pooled the data of the 5 SHS rounds, which enabled us to investigate changes over time. This was done through interpreting the results of the survey variable

Table 1. Demographic characteristic, BMI category, smoking status, and survey.

	Men		Women	
Mean age	**46.0***		**47.9***	
	n	**%***	**n**	**%***
Nationality				
Swiss	28985	79.3	37450	83.4
Foreign	5256	20.7	5100	16.6
Education				
Tertiary	10814	31.0	6772	15.3
Secondary II	19412	56.0	26970	63.7
Mandatory	4015	12.0	8808	21.0
Language region				
German	22761	72.8	27532	71.2
French	9022	22.8	11686	24.0
Italian	2458	4.4	3332	4.8
BMI category				
Underweight	302	0.9	2628	6.3
Normal-weight	17748	52.4	27320	64.7
Overweight	13196	38.3	9263	21.5
Obese	2995	8.4	3339	7.5
Smoking status				
Never	14063	41.3	24431	58.4
Former	9515	26.9	8117	18.6
Light	2799	08.4	3236	7.8
Medium	3100	09.5	3524	8.1
Heavy	4764	13.9	3242	7.1
Survey				
1992	6003	18.8	7574	19.0
1997	5063	19.7	6518	19.8
2002	7389	18.8	9489	19.4
2007	7015	19.7	9064	19.5
2012	8771	23.0	9905	22.3
N Total	34241	100.0	42550	100.0

* weighted according to the general population of Switzerland.

doi:10.1371/journal.pone.0148563.t001

Table 2. Estimated absolute numbers (N) and proportions (%*) for smoking status, BMI, and selected smoking-BMI-combinations in Switzerland 2012.

	Men		Women	
	n	%*	n	%*
BMI				
Underweight	25 771	0.8	193 971	5.8
Normal-weight	1 523 051	47.3	2 061 801	61.4
Overweight	1 296 723	40.3	780 803	23.2
Obese	372 537	11.6	322 836	9.6
Smoking status				
Never	1 466 277	45.6	1 999 815	59.5
Former	888 659	27.6	678 057	20.2
Light	263 114	8.2	271 525	8.1
Medium	295 869	9.2	262 438	7.8
Heavy	304 163	9.4	147 575	4.4
Smoking—BMI—combination				
Normal-weight/ Never smoker	756 523	23.5	1 213 258	36.1
Underweight/ Never smoker	15 485	0.5	119 422	3.6
Overweight/Never smoker	544 589	16.9	460 612	13.7
Obese/ Never smoker	148 484	4.6	202 028	6.0
Normal-weight/ Heavy smoker	138 192	4.3	85 537	2.5
Underweight/ Heavy smoker	3 861	0.1	10 566	0.3
Overweight/Heavy smoker	121 667	3.8	38 493	1.1
Obese/ Heavy smoker	41 910	1.3	14 299	0.4
Total	3 218 082	100.00	3 359 410	100.00

Extrapolation based on SHS 2012 (prevalence) and STATPOP 2012 (Statistics of population and households), permanent resident population aged $\geq$ 18 years, by sex.

* weighted according to the general population of Switzerland.

doi:10.1371/journal.pone.0148563.t002

that was entered into the multinomial regression model. The regression model provided relative risk ratios (RRR) [24].To assess the public health relevance, the absolute number of individuals per BMI category, smoking status, and selected combinations of smoking and BMI were estimated for Switzerland in 2012 by an extrapolation based on SHS 2012 and STATPOP 2012 (Statistics of population and households) [25]. All analyses were performed using STATA 13.1, College Station, TX, USA.

Results

Descriptive

Our analysis included 85,575 individuals. Table 1 shows the distribution of BMI and smoking status categories and demographic characteristics of the study participants by sex (BMI and smoking combinations see S2 Table, lifestyle exposures see S3 Table). Women were on average older than men, whereas there were only negligible differences in nationality and distribution over language regions. The proportion of individuals with tertiary education was twice as high in men compared to women. The prevalence of obesity was comparable in men and women, but the proportion of women with underweight was 6 times higher. Heavy smoking was twice as frequent in men compared to women.

Fig 1 shows the distribution of smoking status by sex for Switzerland in 2012. For heavy and never smoking, combinations with BMI categories are presented in detail. Table 2 shows the corresponding proportions and estimated absolute numbers for Switzerland in 2012. In never and heavy smokers, the proportion of underweight and overweight individuals was comparable in both sexes. However, comparing male never with heavy smokers, the proportion of normal-weight individuals was smaller (never: 52 vs heavy: 45%) whereas the proportion of obese individuals was larger (never: 10 vs heavy: 14%). This difference was smaller in females (61 vs 57%; 10 vs 9%). Sex differences also existed with respect to the prevalence of the combination obesity plus heavy smoking. It was found to be 1.3% in men and 0.5% in women. Men were also more likely to be normal-weight heavy smokers. On the other hand, women were more often obese never smokers, underweight never and heavy smokers, respectively.

Regression analysis

Compared to reference, i.e. normal-weight never smokers, individuals who were normal-weight, obese, or underweight and smoked heavily at the same time had a poorer lifestyle (Table 3); the lifestyle of obese and underweight never smokers differed less from reference. Heavy smokers (referred as smokers in this section) were observed to be more likely to have an unfavourable behaviour with respect to almost all modifiable lifestyle proxy factors, regardless of BMI. In contrast, physical inactivity was the only lifestyle factor that showed an association with being never smoker, except for hazardous alcohol intake in male obese never smokers. The association with the lifestyle factors was shown to be stronger in smokers compared to never smokers. Smokers of both sexes (except for heavy smoking obese women) were most likely to have a high alcohol intake.

The results for smokers by the investigated BMI categories are described in depth as follows. Male normal-weight and obese smokers were likely to have an infrequent fruit and vegetable consumption, low physical inactivity level, and high alcohol intake. For example in men, if an individual reported a low fruit and vegetable consumption, the relative risk ratio for being an obese smoker relative to normal-weight never smoker would be expected to be increased (RRR 1.69 [1.30;2.21]) compared to an individual having a high fruit and vegetable consumption. In underweight smoking men, significant associations were found for physical inactivity and high

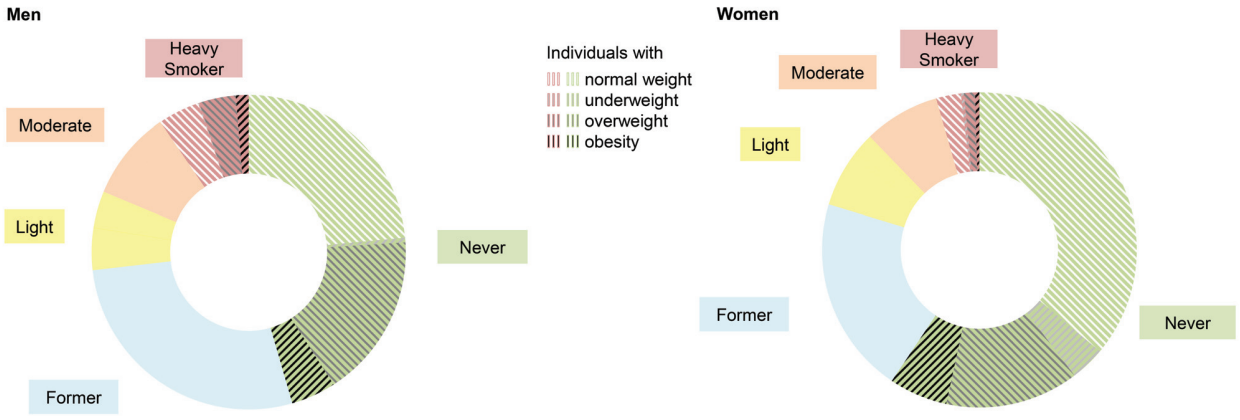

Fig 1. Prevalence of smokers by status additionally stratified by BMI for heavy and never smokers SHS 2012. Men n = 35,880 (missing n = 2,949) and women n = 44,142 (missing n = 2,604). BMI (Body Mass Index, kg/m^2): underweight <18.5, normal-weight ≥18.5–<25, overweight ≥25–<30, obesity ≥30; Smoking status: never, former, light (1–9 cigarettes per day), moderate (10–19), heavy smoker (>19); SHS: Swiss Health Survey; Results are weighted according to the general population of Switzerland.

doi:10.1371/journal.pone.0148563.g001

Table 3. Lifestyle of obese and/or heavy smokers by sex, multinomial logistic regression: reference group normal-weight never smokers (adjusted for sociodemographic factors, age, and survey), weighted according to the general population of Switzerland.

	Normal-weight / Heavy smokers		Obese / Never smokers		Obese / Heavy smokers		Underweight / Never smokers		Underweight / Heavy smokers	
	RRR	(95% CI)	RRR	(95% CI)	RRR	(95% CI)	RRR	(95% CI)	RRR	(95% CI)
Men										
Fruits and vegetables										
Daily	1		1		1		1		1	
< Daily	**1.82**	**(1.62;2.05)**	1.18	(0.99;1.41)	**1.69**	**(1.30;2.21)**	1.21	(0.74;1.98)	1.85	(0.86;3.96)
Physical activity, leisure										
> 2	1		1		1		1		1	
1 to 2	**1.34**	**(1.16;1.56)**	1.23	(0.99;1.52)	1.34	(0.95;1.91)	0.91	(0.52;1.60)	1.11	(0.47;2.62)
Days per week										
None	**2.91**	**(2.50;3.37)**	**1.54**	**(1.24;1.89)**	**3.31**	**(2.38;4.62)**	1.29	(0.72;2.30)	**3.35**	**(1.43;7.87)**
Alcohol*										
Low	1		1		1		1		1	
Moderate	**3.35**	**(2.59;4.35)**	1.18	(0.75;1.86)	**2.15**	**(1.29;3.60)**	1.06	(0.20;5.55)	**5.33**	**(1.59;17.87)**
High	**4.75**	**(3.58;6.31)**	**2.00**	**(1.23;3.25)**	**4.29**	**(2.60;7.07)**	0.24	(0.03;1.76)	**6.83**	**(2.37;19.68)**
Missing	**1.55**	**(1.20;2.00)**	1.36	(0.83;2.22)	1.16	(0.65;2.10)	1.83	(0.53;6.27)	0.62	(0.17;2.18)
Education										
Tertiary	1		1		1		1		1	
Secondary II	**2.04**	**(1.79;2.33)**	**1.74**	**(1.43;2.11)**	**2.86**	**(2.06;3.96)**	**1.93**	**(1.17;3.20)**	**6.97**	**(2.87;16.94)**
Mandatory	**2.19**	**(1.79;2.69)**	**2.67**	**(2.02;3.52)**	**3.26**	**(2.13;4.99)**	**3.53**	**(1.77;7.05)**	**11.67**	**(3.94;34.61)**
Nationality										
Swiss	1		1		1		1		1	
Foreign	**1.43**	**(1.23;1.67)**	**1.60**	**(1.25;2.05)**	**1.51**	**(1.08;2.13)**	1.19	(0.66;2.12)	1.11	(0.44;2.82)
Language region**										
German	1		1		1		1		1	
French	1.01	(0.89;1.15)	0.88	(0.73;1.07)	**0.73**	**(0.55;0.99)**	1.31	(0.77;2.23)	1.24	(0.62;2.48)
Italian	0.83	(0.66;1.04)	1.07	(0.80;1.44)	1.00	(0.64;1.55)	1.41	(0.67;2.95)	0.81	(0.27;2.45)
Survey										
1992	1		1		1		1		1	
1997	1.03	(0.86;1.23)	1.19	(0.84;1.70)	1.10	(0.72;1.69)	1.83	(0.79;4.21)	0.58	(0.22;1.52)
2002	0.86	(0.72;1.03)	**1.58**	**(1.13;2.22)**	1.19	(0.79;1.79)	2.31	(0.99;5.39)	0.81	(0.35;1.90)
2007	**0.60**	**(0.49;0.73)**	**2.12**	**(1.53;2.94)**	0.95	(0.61;1.48)	1.26	(0.51;3.08)	0.40	(0.13;1.25)
2012	**0.47**	**(0.39;0.58)**	**2.54**	**(1.85;3.48)**	1.15	(0.76;1.73)	1.38	(0.58;3.28)	0.52	(0.18;1.50)
Age	1.00	(1.00;1.00)	**1.04**	**(1.03;1.04)**	**1.02**	**(1.01;1.02)**	**0.97**	**(0.95;0.99)**	**0.97**	**(0.95;1.00)**
n		2538		1037		434		121		66
Women										
Fruits and vegetables										
Daily	1		1		1		1		1	
< Daily	**2.48**	**(2.19;2.80)**	0.96	(0.84;1.10)	**1.71**	**(1.22;2.40)**	1.14	(0.98;1.33)	**1.91**	**(1.42;2.56)**
Physical activity, leisure										
> 2	1		1				1		1	
1 to 2	0.86	(0.73;1.02)	1.01	(0.85;1.21)	0.90	(0.54;1.51)	0.96	(0.80;1.15)	0.92	(0.59;1.44)
Days per week										
None	**1.75**	**(1.49;2.06)**	**1.55**	**(1.32;1.83)**	**2.18**	**(1.38;3.43)**	**1.29**	**(1.08;1.54)**	**2.02**	**(1.33;3.08)**
Alcohol*										
Low	1		1		1		1		1	

(*Continued*)

Table 3. (*Continued*)

	Normal-weight / Heavy smokers		Obese / Never smokers		Obese / Heavy smokers		Underweight / Never smokers		Underweight / Heavy smokers	
	RRR	**(95% CI)**	**RRR**	**(95% CI)**	**RRR**	**(95% CI)**	**RRR**	**(95% CI)**	**RRR**	**(95% CI)**
Moderate	**3.50**	**(2.76;4.43)**	0.81	(0.53;1.24)	0.55	(0.22;1.39)	1.07	(0.70;1.63)	**3.42**	**(2.06;5.69)**
High	**5.51**	**(3.71;8.20)**	0.83	(0.40;1.72)	2.19	(0.64;7.49)	0.91	(0.39;2.08)	**5.90**	**(2.54;13.68)**
Missing	**1.47**	**(1.14;1.90)**	1.05	(0.76;1.46)	0.59	(0.18;1.94)	0.95	(0.69;1.32)	1.72	(0.92;3.22)
Education										
Tertiary	1		1				1		1	
Secondary II	**1.91**	**(1.59;2.28)**	**1.78**	**(1.44;2.19)**	**1.83**	**(1.04;3.24)**	**0.78**	**(0.66;0.93)**	1.51	(0.96;2.37)
Mandatory	**2.07**	**(1.67;2.57)**	**3.43**	**(2.73;4.30)**	**4.28**	**(2.33;7.84)**	**0.69**	**(0.54;0.87)**	1.62	(0.95;2.79)
Nationality										
Swiss	1		1		1		1		1	
Foreign	**0.75**	**(0.62;0.90)**	**1.37**	**(1.15;1.65)**	0.67	(0.40;1.13)	**0.69**	**(0.55;0.87)**	0.63	(0.39;1.00)
Language region**										
German	1		1		1		1		1	
French	**1.30**	**(1.14;1.47)**	**0.84**	**(0.73;0.96)**	0.86	(0.60;1.23)	**1.28**	**(1.10;1.50)**	**1.76**	**(1.30;2.39)**
Italian	0.97	(0.79;1.19)	**0.68**	**(0.55;0.85)**	0.79	(0.43;1.43)	**1.58**	**(1.26;1.99)**	0.94	(0.58;1.54)
Survey										
1992	1		1		1		1		1	
1997	**1.23**	**(1.03;1.47)**	**1.37**	**(1.09;1.74)**	**2.56**	**(1.32;4.97)**	0.81	(0.65;1.02)	1.28	(0.81;2.01)
2002	1.01	(0.84;1.21)	**1.58**	**(1.26;1.99)**	**2.31**	**(1.22;4.36)**	0.88	(0.71;1.10)	1.03	(0.66;1.63)
2007	0.93	(0.76;1.13)	**1.84**	**(1.46;2.31)**	1.90	(0.96;3.75)	**0.77**	**(0.61;0.96)**	0.93	(0.56;1.54)
2012	**0.56**	**(0.46;0.70)**	**2.07**	**(1.66;2.59)**	**2.09**	**(1.05;4.15)**	0.93	(0.75;1.15)	**0.50**	**(0.30;0.82)**
Age	**0.98**	**(0.97;0.98)**	**1.03**	**(1.02;1.03)**	0.99	(0.98;1.00)	**0.98**	**(0.97;0.98)**	**0.97**	**(0.96;0.98)**
n		2085		1980		227		1347		313

*Cut-offs: men <40g and <60g and women <20g and <40g of alcohol per day;

**German included Romansh; results shown only for selected combinations of BMI and smoking status.

Missing: BMI n = 1258, smoking status n = 4382, fruits and vegetables n = 1571, physical activity n = 3555, alcohol n = 4966.

doi:10.1371/journal.pone.0148563.t003

risk alcohol intake, despite the small stratum size and therefore wide confidence intervals. Female normal-weight and underweight smokers were likely to have an unfavourable behaviour in all three lifestyle factors. Obese smoking women were more likely to have infrequent fruit and vegetable consumption and high alcohol intake. In contrast to men, women who smoked and/or were underweight or obese were more likely to be physically inactive.

Only a selection of the smoking/BMI combination groups is shown. To briefly summarize the results for the remaining 14 outcome categories, we found that individuals in these categories were less likely to have low fruit and vegetable consumption, high alcohol intake, and physical inactivity, compared to those individuals in the categories with heavy smoking and extreme BMI (not shown). Only overweight heavy smokers showed similar poor behaviour in the three lifestyle variables investigated. In addition, we observed that the lifestyle tended to deteriorate, the more an individual smoked.

Socio-demographic adjustment variables were strongly associated with the combination of heavy smoking and obesity or underweight. In general, individuals with lower educational level were more likely to have an extreme BMI and being a smoker. However, this association was reversed in underweight women. Male foreign nationals were more likely to be normal-weight or obese smokers and obese never smokers, respectively. Being female Swiss national was

associated with being normal-weight smoker or underweight never smoker, whereas foreign nationals were more likely to be obese never smokers. A significant impact of language region was observed mainly in women. Compared to women living in the German speaking part, women from the French and Italian speaking region were more likely to be underweight and less likely to be obese. Moreover, those from the French speaking part were more likely to be underweight smokers.

A decrease in the prevalence of heavy smokers between 1992 and 2012 was observed in those with normal-weight, especially in men (Table 3). Furthermore, the results suggest that the prevalence of the combination of heavy smoking with underweight and obesity changed in women only; it increased in female obese heavy smokers and decreased female underweight heavy smokers. The prevalence of obese never smokers increased in both sexes.

Discussion

Main results

In this study, we investigated how heavy smoking and extreme BMI as well as the combination of both were associated with other NCD risk factors. Heavy smokers were more likely to have a poor diet, high alcohol intake and low level of physical activity than obese or underweight individuals. While the prevalence of smoking decreased over time in combination with normal-weight, it increased in combination with obesity in women.

Clustering of lifestyle factors

In line with our results, studies on clustering effects of unfavourable lifestyle factors in adults emphasise the role of smoking as driving factor [11,26]. The association of smoking was observed to be particularly strong with high alcohol intake [27]. Clustering effects of unhealthy lifestyles were reported to be more likely in individuals with a low educational level [12,13]. In our study, this was consistently shown in men, i.e. smoking and high/low BMI were associated with low educational level. In contrast, this association was reversed in women, i.e. underweight was associated with high educational level. Others showed that men and especially women with higher socioeconomic status were more concerned about their body weight and made more efforts to control it [28,29]. Interestingly, unhealthy behaviours were found to cluster stronger than healthy behaviours [30]. We are not aware of other studies performing a comparative analysis of the lifestyle of heavy smokers, obese, and underweight individuals. However, a study looking at age-specific lifestyle risk factors for obesity observed that young and middle-aged obese adults were frequently physically inactive; in older obese adults, poor eating habits were identified as an additional risk factor [31]. So far, much less has been reported about the lifestyle of underweight individuals because in developed countries the prevalence and, therewith, public health relevance is lower compared to obesity [32]. Reverse causation due to smoking and pre-existing disease has to be taken into account when studying health effects of underweight, e.g. mortality [33,34]. Our findings suggest that underweight never smoking women were at risk for physical inactivity, which could be either an attitude or indicating an underlying disease.

Prevalence trends

We found that the prevalence of normal-weight heavy smokers decreased in Switzerland between 1992 and 2012 in both sexes. Across Europe, considerable differences in smoking prevalence exist; eastern and low income countries as well as countries with less advanced tobacco control policies have highest smoking prevalence [35]. An estimation of smoking

prevalence worldwide showed that it is especially high among men in South, Southeast, and East Asia, e.g. more than 50% in Russia and Indonesia [14]. Our results show that in Switzerland the decrease in smoking prevalence mainly occurred in those with normal BMI; amongst obese individuals, the smoking prevalence stagnated (men) or even increased (women). This suggests that clustering of unhealthy lifestyles persisted or accentuated over time in part of the population, low socioeconomic status was shown to be an important factor explaining this effect [36–38].

Public health relevance

Our results support the notion of smoking as a key determinant of an unhealthy lifestyle. In light of the ongoing clustering of smoking with other unfavourable lifestyle factors, efforts aimed at reducing tobacco use in the population need to be intensified. This is supported by the recent trends of cancer death in women; in Europe lung cancer is the leading cause, thus superseded breast cancer [39]. In Switzerland, previous efforts led to a decrease of the smoking prevalence in general, but a decrease was only observed in the normal-weight part of the population. Because obese and underweight smokers have a particularly problematic health risk pattern, a decrease in smoking prevalence would be even more important than in normal-weight individuals. In Switzerland, obesity contributes to an excess in death of about 7% and costs of 8 billion Swiss Francs; smoking of about 12% and 10 billion Swiss Francs [40–43]. As shown by Li et al. [44], non-smoking and maintaining healthy body weight are the lifestyles with the greatest potential to reduce the number of premature deaths and should therefore be the main target of public health strategies improving lifestyle.

Strengths and Limitations

The SHS is a comprehensive survey collecting data on major lifestyle risk factors through a large representative sample of the general population. The large sample size allowed for the analysis of lifestyle factors in defined risk groups based on BMI category and smoking status. Potential confounders were included in the analysis, especially education. The repeated assessment (the SHS is conducted every 5 years) provided insights into changes over time in prevalence of the considered risk groups.

The participation rate decreased over the 5 SHS from 71% in 1992 to 53% in 2012 [17,45]. Two measures were implemented to account for this decrease in participation rate. First, in 2012 efforts were intensified to include persons having no landline telephone number available in the database, by sending out prepaid answer postcards to obtain further contact information to conduct the telephone interview. Second, analysis of the SHS data has to be done by applying weighting according to the general population of Switzerland. Nevertheless, it is likely that participants tend to be healthier than non-participants [46]. Self-reporting on lifestyle variables made non-differential misclassification of those variables more likely. Only a short questionnaire was used to evaluate fruit and vegetable consumption, alcohol intake and physical activity [47,48]. To draw conclusions, for example on the adherence to the "5-a-day" recommendation, more detailed information would be needed. The assessment of fruit and vegetable consumption was even aggravated by the fact that the collected information changed over the course of surveys and, therefore, it was necessary to use a dichotomized variable. BMI was shown to be underestimated in obese and overestimated in underweight [49]. For underweight, effect estimates were imprecise as strata size was small. Finally, due to the cross-sectional study design no causal relationships can be inferred.

Conclusion

Both heavy smoking and BMI extremes were associated with unhealthy general lifestyle, rendering them particularly vulnerable for NCDs. However, the relationship was stronger for heavy smoking than for obesity and underweight. Smoking prevention measures should pay special attention to improvement of general lifestyle and co-occurrence with obesity and underweight. Future research in this area should focus on how lifestyle factors are interacting in the development of NCDs, i.e. looking at lifestyle patterns rather than single lifestyle risk factors. In addition, investigating the role of lifestyle factors using a life course approach may help to deepen the understanding of their association with NCDs.

Supporting Information

S1 Table. Data Collection on Height, Weight, and Smoking Status, Swiss Health Survey 1992 to 2012.
(DOCX)

S2 Table. Distribution of selected BMI category and Smoking Status Combinations, SHS 1992 to 2012, *weighted according to the Swiss general population.
(DOCX)

S3 Table. Distribution of fruit and vegetable consumption, physical activity, and alcohol intake, SHS 1992 to 2012, *weighted according to the Swiss general population.
(DOCX)

Acknowledgments

We thank the Swiss Cancer Research foundation (SCR) for supporting our study (grant no. KFS-3048-08-2012) and the Swiss Federal Statistical Office for providing data.

Author Contributions

Conceived and designed the experiments: DF SR TL. Analyzed the data: TL. Wrote the paper: TL DF. Critical reading of the manuscript: MB.

References

1. Danaei G, Vander Hoorn S, Lopez AD, Murray CJL, Ezzati M. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005; 366: 1784–93. doi: 10.1016/S0140-6736(05)67725-2 PMID: 16298215
2. Fan J, Song Y, Chen Y, Hui R, Zhang W. Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: a meta-analysis of prospective cohort studies. Int J Cardiol. Elsevier Ireland Ltd; 2013; 168: 4761–8. doi: 10.1016/j.ijcard.2013.07.230
3. Erhardt L. Cigarette smoking: an undertreated risk factor for cardiovascular disease. Atherosclerosis. 2009; 205: 23–32. doi: 10.1016/j.atherosclerosis.2009.01.007 PMID: 19217623
4. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer : a systematic review and meta-analysis of prospective observational studies. Lancet. 2007; 569–578.
5. Loprinzi PD, Crespo CJ, Andersen RE, Smit E. Association of Body Mass Index with Cardiovascular Disease Biomarkers. Am J Prev Med. Elsevier; 2014; 1–7. doi: 10.1016/j.amepre.2014.08.019
6. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-Specific Excess Deaths Associated With Underweight, Overweight, and Obesity. JAMA. 2007; 298: 2028–37. doi: 10.1001/jama.298.17.2028 PMID: 17986696
7. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004; 328: 1519. doi: 10.1136/bmj.38142.554479.AE PMID: 15213107
8. Ma J, Jemal A, Flanders WD, Ward EM. Joint association of adiposity and smoking with mortality among U.S. adults. Prev Med (Baltim). 2013; 56: 178–84. doi: 10.1016/j.ypmed.2012.12.012

9. Loef M, Walach H. The combined effects of healthy lifestyle behaviors on all cause mortality: a systematic review and meta-analysis. Prev Med (Baltim). Elsevier Inc.; 2012; 55: 163–70. doi: 10.1016/j.ypmed.2012.06.017
10. Martin-Diener E, Meyer J, Braun J, Tarnutzer S, Faeh D, Rohrmann S, et al. The combined effect on survival of four main behavioural risk factors for non-communicable diseases. Prev Med (Baltim). Elsevier Inc.; 2014; 65: 148–152. doi: 10.1016/j.ypmed.2014.05.023
11. Chiolero A, Wietlisbach V, Ruffieux C, Paccaud F, Cornuz J. Clustering of risk behaviors with cigarette consumption: A population-based survey. Prev Med (Baltim). 2006; 42: 348–53. doi: 10.1016/j.ypmed.2006.01.011
12. Schuit AJ, van Loon AJM, Tijhuis M, Ocké MC. Clustering of Lifestyle Risk Factors in a General Adult Population. Prev Med (Baltim). 2002; 35: 219–224. doi: 10.1006/pmed.2002.1064
13. De Vries H, van 't Riet J, Spigt M, Metsemakers J, van den Akker M, Vermunt JK, et al. Clusters of lifestyle behaviors: results from the Dutch SMILE study. Prev Med (Baltim). 2008; 46: 203–8. doi: 10.1016/j.ypmed.2007.08.005
14. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. JAMA. American Medical Association; 2014; 311: 183–92. doi: 10.1001/jama.2013.284692
15. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384. doi: 10.1016/S0140-6736(14)60460-8
16. Roh L, Braun J, Chiolero A, Bopp M, Rohrmann S, Faeh D. Mortality risk associated with underweight: a census-linked cohort of 31,578 individuals with up to 32 years of follow-up. BMC Public Health. 2014; 14: 371. doi: 10.1186/1471-2458-14-371 PMID: 24739374
17. Bundesamt für Statistik. Die Schweizerische Gesundheitsbefragung 2012 in Kürze—Konzept, Methode, Durchführung. 2013. Available: http://www.bfs.admin.ch
18. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. Obes Res. 1998.
19. WHO. Fruit and Vegetable Promotion Initiative—report of the meeting. Geneva;
20. Wanner M, Tarnutzer S, Martin BW, Braun J, Rohrmann S, Bopp M, et al. Impact of different domains of physical activity on cause-specific mortality: a longitudinal study. Prev Med (Baltim). Elsevier Inc.; 2014; 62: 89–95. doi: 10.1016/j.ypmed.2014.01.025
21. UNESCO Institute for Statistics. International Standard Classification of Education—ISCED 2011. Motreal; 2012.
22. Bottorff JL, Haines-Saah R, Oliffe JL, Sarbit G. Gender influences in tobacco use and cessation interventions. Nurs Clin North Am. 2012; 47: 55–70. doi: 10.1016/j.cnur.2011.10.010 PMID: 22289398
23. Higgins ST, Kurti AN, Redner R, White TJ, Gaalema DE, Roberts ME, et al. A literature review on prevalence of gender differences and intersections with other vulnerabilities to tobacco use in the United States, 2004–2014. Prev Med (Baltim). 2015; doi: 10.1016/j.ypmed.2015.06.009
24. Hosmer D, Lemeshow S. Applied Logistic Regression. Second Edi. New York: John Wiley & Sons; 2000.
25. Bundesamt für Statistik. Statistik der Bevölkerung und der Haushalte (STATPOP). 2012. Available: http://www.bfs.admin.ch
26. Dallongeville J, Mare N, Fruchart J, Amouyel P. Cigarette Smoking Is Associated with Unhealthy Patterns of Nutrient Intake: a Meta-analysis. Am Soc Nutr Sci. 1998; 128: 1450–1457.
27. De Leon J, Rendon DM, Baca-Garcia E, Aizpuru F, Gonzalez-Pinto A, Anitua C, et al. Association between smoking and alcohol use in the general population: Stable and unstable odds ratios across two years in two different countries. Alcohol Alcohol. 2007; 42: 252–257. doi: 10.1093/alcalc/agm029 PMID: 17526636
28. Wardle J, Griffith J. Socioeconomic status and weight control practicesin British adults. J Epidemiol Community Heal. 2001; 55: 185–190. doi: 10.1136/jech.55.3.185
29. Choi OJE, Cho YG, Kang JH, Park HA, Kim KW, Hur YI, et al. Weight control attempts in underweight korean adults: Korea national health and nutrition examination survey, 2007–2010. Korean J Fam Med. 2013; 34: 393–402. doi: 10.4082/kjfm.2013.34.6.393 PMID: 24340161
30. Tobias M, Jackson G, Yeh L-C, Huang K. Do healthy and unhealthy behaviours cluster in New Zealand? Aust N Z J Public Health. 2007; 31: 155–163. doi: 10.1111/j.1753-6405.2007.00034.x PMID: 17461007
31. Siddarth D. Risk factors for obesity in children and adults. J Investig Med. 2013; 61: 1039–42. doi: 10.231/JIM.0b013e31829c39d0 PMID: 23838696

32. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999; 341: 1097–105. doi: 10.1056/NEJM199910073411501 PMID: 10511607

33. Flegal KM, Graubard BI, Williamson DF, Cooper RS. Reverse causation and illness-related weight loss in observational studies of body weight and mortality. Am J Epidemiol. 2011; 173: 1–9. doi: 10.1093/aje/kwq341 PMID: 21059807

34. Willett WC, Dietz WH, Colditz GA. Guidelines for Healthy Weight. N Engl J Med. 1999; 341: 427–434. doi: 10.1056/NEJM199908053410607 PMID: 10432328

35. Gallus S, Lugo A, La Vecchia C, Boffetta P, Chaloupka FJ, Colombo P, et al. Pricing Policies And Control of Tobacco in Europe (PPACTE) project: cross-national comparison of smoking prevalence in 18 European countries. Eur J Cancer Prev. 2014; 23: 177–85. doi: 10.1097/CEJ.0000000000000009 PMID: 24441832

36. Buck D, Frosini F. Clustering of unhealthy behaviours over time—Implications for policy and practice. London; 2012.

37. Marques-Vidal P, Bovet P, Paccaud F, Chiolero A. Changes of overweight and obesity in the adult Swiss population according to educational level, from 1992 to 2007. BMC Public Health. 2010; 10: 87. doi: 10.1186/1471-2458-10-87 PMID: 20170554

38. Faeh D, Braun J, Bopp M. Prevalence of obesity in Switzerland 1992–2007: the impact of education, income and occupational class. Obes Rev. 2010; 12: 151–66. doi: 10.1111/j.1467-789X.2010.00793.x

39. Malvezzi M, Bertuccio P, Rosso T, Rota M, Levi F, Vecchia C La, et al. European cancer mortality predictions for the year 2015 : does lung cancer have the highest death rate in EU women ? Ann Oncol. 2015; 00: 1–8. doi: 10.1093/annonc/mdv001

40. Faeh D, Braun J, Tarnutzer S, Bopp M. Obesity but not overweight is associated with increased mortality risk. Eur J Epidemiol. 2011; 26: 647–55. doi: 10.1007/s10654-011-9593-2 PMID: 21681546

41. Maag J, Braun J, Bopp M, Faeh D. Direct estimation of death attributable to smoking in Switzerland based on record linkage of routine and observational data. Nicotine Tob Res. 2013; 15: 1588–97. doi: 10.1093/ntr/ntt023 PMID: 23493371

42. Wieser S, Kauer L, Schmidhauser S, Pletscher M, Brügger U, Jeanrenaud C, et al. Synthesebericht–Ökonomische Evaluation von Präventionsmassnahmen in der Schweiz. Winterthur; 2010. Available: http://www.bag.admin.ch

43. Schneider H, Venetz W. Cost of Obesity in Switzerland in 2012. Rheinfelden; 2014. Available: http://www.bag.admin.ch

44. Li K, Hüsing A, Kaaks R. Lifestyle risk factors and residual life expectancy at age 40: a German cohort study. BMC Med. 2014; 12: 59. doi: 10.1186/1741-7015-12-59 PMID: 24708705

45. Faeh D, Bopp M. Excess weight in the canton of Zurich, 1992–2009: Harbinger of a trend reversal in Switzerland? Swiss Med Wkly. 2010; 140: 1–6. doi: 10.4414/smw.2010.13090

46. Bopp M, Braun J, Faeh D, National S, Study C. Practice of Epidemiology Variation in Mortality Patterns Among the General Population, Study Participants, and Different Types of Nonparticipants : Evidence From 25 Years of Follow-up. Am J Epidemiol. 2014; 180: 1028–1035.

47. Eichholzer M, Bisig B. Daily consumption of (red) meat or meat products in Switzerland: results of the 1992/93 Swiss Health Survey. Eur J Clin Nutr. 2000; 54: 136–142. doi: 10.1038/sj.ejcn.1600907 PMID: 10694784

48. Rehm J, Spuhler T. Measurement error in alcohol consumption: the Swiss Health Survey. Eur J Clin Nutr. 1993; 47: S25–S30.

49. Stommel M, Schoenborn C. Accuracy and usefulness of BMI measures based on self-reported weight and height: findings from the NHANES & NHIS 2001–2006. BMC Public Health. 2009; 9: 421. doi: 10.1186/1471-2458-9-421 PMID: 19922675

S1 Table. Data Collection on Height, Weight, and Smoking Status; Swiss Health Survey 1992 to 2012.

Height and weight									
Nr.	**Fragen**	**Thema**	**Modul**	**1992**	**1997**	**2002**	**2007**	**2012**	**Quelle / Bemerkungen**
23.00	WIEDER AN ALLE Können Sie mir sagen, wie gross Sie ohne Schuhe sind? ---------- - Zentimeter *(3-stellig)* ..... _ _ _ ---------- - Weiss nicht..... (-1) - Keine Antwort..... (-2)	Gesundheitszustand Körpermasse TGEZU01b	Kern	1	1	1	1	1	IGIP tel. 54.00 *SGB07: TGEZU01a entfernt, da überflüssig.*
23.10	Und wie schwer sind Sie ohne Kleider? BEI SCHWANGEREN FRAUEN (22.00 = 1): Wie schwer sind Sie am Anfang von der Schwangerschaft gewesen? ---------- - Kilos *(3-stellig)* ..... _ _ _ ---------- - Weiss nicht..... (-1) - Keine Antwort..... (-2)	Gesundheitszustand Körpermasse TGEZU02b	Kern	1	1	1	1	1	IGIP tel. 55.00 *SGB07: TGEZU02a entfernt, da überflüssig*
Smoking									
39.00	Rauchen Sie, wenn auch nur selten? ---------- - Ja..... 1 - Nein ..... 2 weiter zu 39.20 ---------- - Keine Antwort..... (-2) weiter zu 39.20	Tabakkonsum TTAKO01	Kern	1	1	1	1	1	Anal. IGIP tel. 28.00
39.01	Rauchen Sie täglich? ---------- - Ja..... 1 - Nein ..... 2 ---------- - Keine Antwort..... (-2)	Tabakkonsum TTAKO21	Kern	0	0	0	1	1	EHIS angepasst
39.10	Was rauchen Sie? *INT: Vorlesen!* ---------- - Zigaretten..... Ja=1 Nein=2 Keine Antwort=(-2) - Zigarren ..... Ja=1 Nein=2 Keine Antwort=(-2) - Cigarillos ..... Ja=1 Nein=2 Keine Antwort=(-2) - Pfeife..... Ja=1 Nein=2 Keine Antwort=(-2) - Wasserpfeife ..... Ja=1 Nein=2 Keine Antwort=(-2)	Tabakkonsum TTAKO02a TTAKO02b TTAKO02c TTAKO02d TTAKO02e	Kern	1	1	1	1	1	IGIP tel. 28.10 *SGB07 mit TTAKO02e ergänzt*

S1 Table. Data Collection on Height, Weight, and Smoking Status; Swiss Health Survey 1992 to 2012, continued.

39.11	PERSONEN, DIE ZIGARETTEN RAUCHEN (TTAKO02A/39.10=1) Wieviele Zigaretten rauchen Sie im Durchschnitt pro Tag? *INT: 1 Paket = 20 Zigaretten / 1/2Paket =10 Zigaretten* ---------- - Zigaretten *(2-stellig)* ....._ _ - Weniger als 1 pro Tag....00 ---------- - Keine Antwort....(-2)	Tabakkonsum TTAKO03	Kern	1	1	1	1	1	IGIP tel. 28.11
39.12	PERSONEN, DIE ZIGARREN RAUCHEN (TTAKO02B/39.10=1) Wie viele Zigarren rauchen Sie im Durchschnitt pro Tag? ---------- - Zigarren *(2-stellig)* ....._ _ - Weniger als 1 pro Tag....00 ---------- - Keine Antwort....(-2)	Tabakkonsum TTAKO04	Kern	1	1	1	1	1	IGIP tel. 28.12
Nr.	**Fragen**	**Thema**	**Modul**	**1992**	**1997**	**2002**	**2007**	**2012**	**Quelle / Bemerkungen**
39.13	PERSONEN, DIE CIGARILLOS RAUCHEN (TTAKO02C/39.10=1) Wie viele Cigarillos rauchen Sie im Durchschnitt pro Tag? ---------- - Cigarillos *(2-stellig)*....._ _ - Weniger als 1 pro Tag....00 ---------- - Keine Antwort....(-2)	Tabakkonsum TTAKO05	Kern	1	1	1	1	1	IGIP tel. 28.13
39.14	PERSONEN, DIE PFEIFE RAUCHEN (TTAKO02D/39.10=1) Wie viele Pfeifen rauchen Sie im Durchschnitt pro Tag? ---------- - Pfeifen *(2-stellig)* ....._ _ - Weniger als 1 pro Tag....00 ---------- - Keine Antwort....(-2)	Tabakkonsum TTAKO06	Kern	1	1	1	1	1	IGIP tel. 28.14
Nr.	**Fragen**	**Thema**	**Modul**	**1992**	**1997**	**2002**	**2007**	**2012**	**Quelle / Bemerkungen**
39.20	NUR NICHTRAUCHER/INNEN (+KA) (TTAKO01/39.00=2, -2). RAUCHER/INNEN WEITER ZU FRAGE 39.30 Haben Sie je regelmässig während mehr als 6 Monaten geraucht? ---------- - Ja.... 1 - Nein .... 2 weiter zu 39.50 ---------- - Keine Antwort....(-2) weiter zu 39.50	Tabakkonsum TTAKO07	Kern	1	1	1	1	1	IGIP tel. 28.30

S2 Table. Distribution of selected BMI category and Smoking Status Combinations, SHS 1992 to 2012, *weighted according to the Swiss general population.

	Men		Women	
	n	%*	n	%*
Smoking - BMI - combination				
Normal-weight/ Never smoker	9106	25.4	16850	38.5
Normal-weight/ Heavy smoker	2595	6.8	2131	4.2
Obese/ Never smoker	1124	3.0	2108	4.6
Obese/ Heavy smoker	441	1.2	234	0.4
Underweight/ Never smoker	273	0.9	1651	4.0
Underweight/ Heavy smoker	69	0.2	328	0.6
Total	37152	100.00	45395	100.00

S3 Table. Distribution of fruit and vegetable consumption, physical activity, and alcohol intake, SHS 1992 to 2012, *weighted according to the Swiss general population.

	Men		Women	
	n	%*	n	%*
Fruit and vegetable consumption				
Daily	19022	50.9	32409	70.5
< Daily	18875	49.1	13698	29.5
Physical activity, leisure time, days per week				
>2	11068	30.8	10449	23.7
1 to 2	13501	37.2	15605	35.0
None	12175	32.0	19222	41.3
Alcohol intake				
Low	33465	86.0	42180	90.1
Moderate	1622	4.0	1531	3.1
High	1343	3.2	468	1.0
Missing	2399	6.8	2567	5.8
Total	37152	100.00	45395	100.00

Paper III

Continuous Outcome Logistic Regression for Analyzing Body Mass Index Distributions

Tina Lohse, Sabine Rohrmann, David Faeh, Torsten Hothorn

Under Review

Continuous Outcome Logistic Regression for Analyzing Body Mass Index Distributions

Tina Lohse **Sabine Rohrmann** **David Faeh** **Torsten Hothorn**

Abstract

Body Mass Index (BMI) categories are used to monitor weight status and associated health risks in populations. Binary or multinomial logistic regression models are commonly applied in this context but are only applicable to BMI values categorized within a small set of defined ad hoc BMI categories. This approach precludes comparisons with studies and models based on different categories, which renders meta analyses difficult. In addition, ad hoc categorization of BMI values prevents the estimation and analysis of the underlying continuous BMI distribution and leads to information loss. As an alternative to multinomial regression following ad hoc categorization, we propose a continuous outcome logistic regression model for the estimation of a continuous BMI distribution. Parameters of interest, such as odds ratios for specific categories, can be extracted from this model post hoc in a general way. A continuous BMI logistic regression that describes BMI distributions avoids the necessity of ad hoc and post hoc category choice and simplifies between-study comparisons and pooling of studies for joint analyses. The method was evaluated empirically using data from the Swiss Health Survey.

Keywords: Distribution regression, transformation model, conditional distribution, odds ratio, smoking.

Body mass index (BMI) is an anthropometric measure that is relatively easy to capture in epidemiological studies. Thus, it is widely used for describing underweight, overweight, and obesity (Wells and Fewtrell 2006; Ng *et al.* 2014). The most prominent standard BMI categories underweight, normal weight, overweight, and obesity as defined by the World Health Organization (WHO, World Health Organization 2000) are commonly applied to ensure comparability and reproducibility of statistical analyses across epidemiological studies (Flegal *et al.* 2013, 2014). Such international standards are important for the communication of scientific results, for risk factor assessment and monitoring in populations, and for providing information to the general public. However, categorization of BMI values inevitably leads to information loss because an individual's weight and height can be measured precisely using simple tools (Wells and Fewtrell 2006), but this precision is lost in statistical analyses by such an ad hoc categorization (Altman and Royston 2004). The most important problem, however, is the lack of comparability across studies that rely on different categorization schemes. Even more troublesome is the problem of comparability of studies and findings over time because the WHO categories can be expected to be updated to better reflect contemporary BMI distributions. Only roughly half of the studies published up to 2000 that used BMI as a risk factor for death used the WHO categories; the other half relied on a variety of different alternative schemes (Flegal *et al.* 2013, 2014). The same problem occurs when the primary interest in a statistical analysis is the comparison of BMI distributions between different risk

groups. In this latter situation, we advocate post hoc categorization of model outputs instead of ad hoc categorization of BMI measurements to better combine measurement precision, ease of communication, comparability, and reproducibility. Specifically, we propose that statistical analyses should be based on precise BMI measurements without ad hoc categorization, and then parameters and interesting contrasts thereof should then be categorized post hoc. Such results would be interpretable and universally comparable between studies using any type of category.

Conceptually, the traditional approaches to the analysis of BMI can be understood as regression models for the conditional distribution of BMI, given exposure, sex, and covariates (Chang and Christakis 2003; Chiolero *et al.* 2007; John *et al.* 2005; Clair *et al.* 2011; Mackay *et al.* 2013; Dare *et al.* 2015; Mead *et al.* 2016). For example, restricting the only exposure variable to smoking in the following, the generic logistic regression model (Agresti 2013) for BMI, conditional on smoking status, sex, and covariates $\boldsymbol{x}$ of the form

$$\operatorname{logit}(\mathbb{P}(\text{BMI} \leq b \mid \text{smoking}, \text{sex}, \boldsymbol{x})) = r(b \mid \text{smoking}, \text{sex}, \boldsymbol{x}) \tag{1}$$

can be used to understand the impact of these variables on the distribution of BMI. After ad hoc categorization, only the conditional distribution of BMI at the corresponding cut-off points b can be evaluated. This also corresponds to a specific parameterization of the regression function r. The core idea of continuous outcome logistic regression is to model the entire conditional distribution of BMI for all reasonable BMI values simultaneously. This requires that the parameterization of the regression function r is a smooth and monotonically increasing function of b. Sex, smoking status, and covariates $\boldsymbol{x}$ then have an impact on the regression function r and thus on conceptually all moments (mean, variance, skewness, kurtosis, etc.) of the conditional continuous BMI distribution.

The interpretation of parameters and contrasts thereof in this more general model is as simple as in models based on specific categories. For example, the difference between $r(b \mid \text{former smoker}, \text{female}, \boldsymbol{x})$ and $r(b \mid \text{never smoker}, \text{female}, \boldsymbol{x})$ is the log-odds ratio of the event BMI $\leq b$ of former female smokers compared to females who never smoked, both of which share the same covariate status $\boldsymbol{x}$. After traditional ad hoc categorization, this odds ratio can only be evaluated for the small set of cut-off points b that define the categories. For continuous outcome logistic regression, the odds ratio can be evaluated for all potential BMI values $b > 0$, which allows the associations for different categorization schemes to be interpreted post hoc. This feature ensures comparability and reproducibility independent of any ad hoc choice of categories.

The continuous outcome logistic regression model can be estimated by maximum likelihood for BMI measurements recorded at different scales. The likelihood contribution of an individual with a BMI value in the interval $(\underline{b}, \bar{b}]$ is simply the probability, in light of some specific regression function r, of observing a BMI within this interval (Lindsey 1996)

$$\begin{aligned} &\mathbb{P}(\underline{b} < \text{BMI} \leq \bar{b} \mid \text{smoking}, \text{sex}, \boldsymbol{x}) \\ &\quad = \mathbb{P}(\text{BMI} \leq \bar{b} \mid \text{smoking}, \text{sex}, \boldsymbol{x}) - \mathbb{P}(\text{BMI} \leq \underline{b} \mid \text{smoking}, \text{sex}, \boldsymbol{x}) \\ &\quad = \operatorname{expit}(r(\bar{b} \mid \text{smoking}, \text{sex}, \boldsymbol{x})) - \operatorname{expit}(r(\underline{b} \mid \text{smoking}, \text{sex}, \boldsymbol{x})). \end{aligned} \tag{2}$$

The BMI measurement $(\underline{b}, \bar{b}]$ can be a narrow numeric interval based on precise measurements of height and weight, or a wide interval corresponding to some standard or non-standard categorization scheme. Thus, continuous outcome logistic regression is applicable to studies that

implement different BMI measurement scales or categorization schemes, or even a mixture of those. The procedure thus directly addresses the conceptual problem of lack of comparability between different studies.

The aim of our study was to propose a continuous outcome logistic regression model for BMI that is independent of both the BMI measurement scale and cut-offs used for ad hoc categorization, which would allow tailored categorized parameters and contrasts to be extracted, compared, and communicated post hoc. We expected the model to be insensitive to the BMI measurement scales, in light of both the estimated conditional BMI distributions and the covariate model parameters. We evaluated this hypothesis empirically by analyzing the association of smoking status and BMI using data from the Swiss Health Survey 2012 (Bundesamt für Statistik 2013) while controlling for important covariates, such as age, alcohol intake, diet, physical activity, and socio-economic variables. We compared models fitted to a cascade of increasingly precise BMI values, starting with the four WHO categories and ending with the "exact" BMI values. This allowed an understanding of the impact of the measurement scale on the resulting models. We also expected the results of the novel continuous outcome logistic model for BMI to be comparable to previously reported associations of smoking and BMI, and evaluated this hypothesis for the Swiss Health Survey 2012.

Methods

Population for Empirical Evaluation

The Swiss Health Survey (SHS) is a population-based cross-sectional survey. Since 1992, it has been conducted every five years by the Swiss Federal Statistical Office (Bundesamt für Statistik 2013). For this study, we restricted the sample from the 2012 survey to 16,427 individuals aged between 18 and 74 years. Height and weight were self-reported by telephone interview. Records with extreme values of height or weight were excluded (highest and lowest percentile by sex). Smoking status was categorized into never smoked, former smokers, light smokers($1-9$ cigarettes per day), moderate smokers($10-19$), and heavy smokers (>19). Individuals who never smoked stated that they did not currently smoke and never regularly smoked for longer than a six-month period; former smokers had quit smoking but had smoked for more than 6 months during their life. One cigarillo or pipe was counted as two cigarettes, and one cigar was counted as four cigarettes. The following adjustment variables were included: fruit and vegetable consumption, physical activity, and alcohol intake. Information on the number of days per week fruits and vegetables were consumed was available. We chose to categorize as close to the "5-a-day" recommendation as possible (World Health Organization 2003). Fruit and vegetable consumption was combined in one binary variable that comprised the information on whether both fruits and vegetables were consumed daily or not. The variable describing physical activity was defined as the number of days per week a subject started to sweat during leisure time physical activity and was categorized as >2 days, $1-2$ days, or none. Alcohol intake was included using the continuous variable grams per day. Education was included as highest degree obtained and was categorized as mandatory (International Standard Classification of Education, ISCED 1-2), secondary II (ISCED 3-4), or tertiary (ISCED 5-8) (UNESCO Institute for Statistics 2012). Nationality had the two categories Swiss and foreign. Language region reflecting cultural differences within Switzerland

was categorized as German/Romansh, French, or Italian.

Models for BMI Distributions

Binary logistic regression, ordered, and unordered polytomous logistic regression (Agresti 2013) were previously applied to the analysis of BMI distributions based on ad hoc categorized BMI values. We will review the corresponding parameterizations and compare the model parameters in the common framework of model (1) before introducing the novel continuous outcome logistic regression for the analysis of BMI distributions.

Binary Logistic Regression For a binary outcome, such as non-obesity vs. obesity ($\text{BMI}_{30} = I(\text{BMI} \leq 30)$), the regression function is defined for non-obese individuals only

$$r(30 \mid \text{smoking}, \text{sex}, \boldsymbol{x}) = \alpha_{30} + \boldsymbol{\gamma}_{\text{smoking:sex}} + \boldsymbol{x}^\top \boldsymbol{\beta},$$

with intercept α_{30}, main and interaction parameters $\boldsymbol{\gamma}$ of smoking and sex, and regression coefficients or covariate parameters $\boldsymbol{\beta}$. This model evaluates the conditional distribution function for BMI only at $b = 30$. Note that a change of the BMI cut-off point b leads to a different model and thus different parameter estimates for *all* parameters α_b, $\boldsymbol{\gamma}$, and $\boldsymbol{\beta}$. Such models have been reported for $b = 25$ or $b = 30$ Mackay *et al.* (2013); Dare *et al.* (2015).

Ordered Polytomous Logistic Regression This model is also known as proportional odds logistic regression for an ordered categorical outcome, such as the WHO categories (World Health Organization 2000) underweight ($\text{BMI}_{18.5} = I(\text{BMI} \leq 18.5)$), normal weight ($\text{BMI}_{(18.5,25]} = I(18.5 < \text{BMI} \leq 25)$), overweight ($\text{BMI}_{(25,30]} = I(25 < \text{BMI} \leq 30)$), and obese ($\text{BMI} > 30$). For these four categories, the model is defined by three category-specific regression functions

$$\begin{aligned} r(18.5 \mid \text{smoking}, \text{sex}, \boldsymbol{x}) &= \alpha_{18.5} + \boldsymbol{\gamma}_{\text{smoking:sex}} + \boldsymbol{x}^\top \boldsymbol{\beta} \\ r(25 \mid \text{smoking}, \text{sex}, \boldsymbol{x}) &= \alpha_{(18.5,25]} + \boldsymbol{\gamma}_{\text{smoking:sex}} + \boldsymbol{x}^\top \boldsymbol{\beta} \\ r(30 \mid \text{smoking}, \text{sex}, \boldsymbol{x}) &= \alpha_{(25,30]} + \boldsymbol{\gamma}_{\text{smoking:sex}} + \boldsymbol{x}^\top \boldsymbol{\beta} \end{aligned}$$

or, in more compact notation, by $r(b \mid \text{smoking}, \text{sex}, \boldsymbol{x}) = \alpha(b) + \boldsymbol{\gamma}_{\text{smoking:sex}} + \boldsymbol{x}^\top \boldsymbol{\beta}$ with intercept function

$$\alpha(b) = \begin{cases} \alpha_{18.5} & b \leq 18.5 \\ \alpha_{(18.5,25]} & 18.5 < b \leq 25 \\ \alpha_{(25,30]} & 25 < b \leq 30. \end{cases} \tag{3}$$

The parameters $\boldsymbol{\gamma}$ and $\boldsymbol{\beta}$ are the same for all three regression functions and can be interpreted as category-independent log-odds ratios as a consequence of the proportional odds assumption on these parameters. The intercept function increases monotonically. Ordered polytomous logistic regression can be understood as a series of binary logistic regression models where only the intercept is allowed to change with increasing BMI values at cut-off points chosen ad hoc. Self-reported BMI values using the WHO criteria

have been analyzed by such a model in Chang and Christakis (2003). The BMI distribution of children categorized at marginal percentiles has been analyzed by a proportional odds model in (Mead *et al.* 2016).

Unordered Polytomous Logistic Regression Multinomial logistic regression is equivalent to polytomous logistic regression for an unordered outcome and is a generalization of the proportional odds model as it allows for category-specific parameters $\boldsymbol{\gamma}(b)$ and $\boldsymbol{\beta}(b)$ in the regression function

$$r(b \mid \text{smoking}, \text{sex}, \boldsymbol{x}) = \alpha(b) + \boldsymbol{\gamma}(b)_{\text{smoking:sex}} + \boldsymbol{x}^\top \boldsymbol{\beta}(b)$$

for $b \in \{18.5, 25, 30\}$. The model can be used to test the proportional odds assumption, *i.e.,* $\boldsymbol{\gamma} \equiv \boldsymbol{\gamma}(b)$ and $\boldsymbol{\beta} \equiv \boldsymbol{\beta}(b)$ for all $b \in \{18.5, 25, 30\}$. Typically, the model is introduced as a model of the conditional density by the relationship between density and distribution function for discrete variables (as in (2)). This model is very popular for the analysis of BMI-related outcomes (Chiolero *et al.* 2007; John *et al.* 2005; Clair *et al.* 2011).

The novel continuous outcome logistic regression model can be viewed as a generalization of the above-introduced models from discrete to continuous outcomes. BMI is understood as a conceptually continuous variable, regardless of the scale of the actual BMI measurements. The most important aspect here is a smooth and monotonically increasing intercept function $\alpha(b)$. In an unconditional model for the marginal BMI distribution

$$\text{logit}(\mathbb{P}(\text{BMI} \leq b)) = r(b) = \alpha(b),$$

, such an intercept function can model arbitrary BMI distribution functions by the term $\text{expit}(\alpha(b))$. This essentially removes the need to specify a strict parametric distribution, such as the normal, for BMI. Because of a potential impact of both smoking and sex of the individual on the entire distribution, we stratify this intercept function with respect to these two variables, *i.e.,* one specific intercept function is dedicated to each combination of smoking and sex:

$$\text{logit}(\mathbb{P}(\text{BMI} \leq b \mid \text{smoking}, \text{sex})) = r(b \mid \text{smoking}, \text{sex}) = \alpha(b)_{\text{smoking:sex}}.$$

To facilitate model interpretation, we assume that regression coefficients $\boldsymbol{\beta}$ of the remaining covariates are constant across the entire BMI distribution in our final model

$$\begin{aligned} \text{logit}(\mathbb{P}(\text{BMI} \leq b \mid \text{smoking}, \text{sex}, \boldsymbol{x})) &= r(b \mid \text{smoking}, \text{sex}) \\ &= \alpha(b)_{\text{smoking:sex}} + \boldsymbol{x}^\top \boldsymbol{\beta}. \end{aligned} \tag{4}$$

The regression coefficients $\boldsymbol{\beta}$ are log-odds ratios of *all* possible events $\text{BMI} \leq b, b > 0$. The interpretation of the parameters $\boldsymbol{\beta}$ is the same in logistic regression, proportional odds regression, and the novel continuous BMI logistic regression (4). This model can be understood as a joint model of all possible binary logistic regression models for the outcomes $\text{BMI} \leq b$ with $b > 0$ under two constraints: (1) the sex- and smoking-level-specific intercept is not allowed to jump abruptly and increases for increasing cut-off points b; (2) the regression coefficients $\boldsymbol{\beta}$ are held constant as b increases. Instead of restricting our attention to specific binary logistic

regression models defined by some cut-off points chosen ad hoc, we can answer questions about the odds ratios for all or specific events BMI $\leq b$ post hoc based on this model.

The interpretation of the sex- and smoking-specific intercept functions, and thus the associations of smoking and sex with BMI, however, is fundamentally different from the interpretation of the regression coefficients $\boldsymbol{\beta}$. Because we allow the entire BMI distribution to change with these two variables in more complex ways, there is no simple interaction term $\boldsymbol{\gamma}$ that captures these parameters in model (4). However, model (4) allows computation of the log-odds ratios for some event BMI $\leq b$ between, for example, female former smokers and females who never smoked for all $\boldsymbol{x}$ as

$$\begin{aligned} & r(b \mid \text{former smoker}, \text{female}, \boldsymbol{x}) - r(b \mid \text{never smoked}, \text{female}, \boldsymbol{x}) \\ = \;& \alpha(b)_{\text{former smoker:female}} - \alpha(b)_{\text{never smoked:female}} \end{aligned}$$

In this way, the parameters and contrasts we are interested in are not directly parameterized in model (4) but nevertheless can be obtained from this model by relatively simple contrasts. The events BMI $\leq b$ are not restricted to those of a specific categorization of the BMI measurements (such as the WHO categories). Due to the smoothness of the underlying intercept functions, log-odds ratios can be computed for arbitrary BMI values $b > 0$.

Likelihoods for BMI Models

Because the regression function r is defined for all possible BMI values b in model (4), the likelihood (2) can be evaluated for all types of intervals $(\underline{b}, \bar{b}]$ and also for "exact" BMI values computed as the ratio of weight and squared height. We distinguished between four different likelihood contributions corresponding to four different BMI measurement scales.

WHO Categories (WHO) The BMI for each individual was reported in one of the four WHO categories corresponding to the intervals ≤ 18.5 (underweight), $(18.5, 25]$ (normal weight), $(25, 30]$ (overweight), > 30 (obese). The likelihood contribution of a normal-weight individual is thus

$$\begin{aligned} & \mathbb{P}(18.5 < \text{BMI} \leq 25 \mid \text{smoking}, \text{sex}, \boldsymbol{x}) = \\ & \text{expit}(r(25 \mid \text{smoking}, \text{sex}, \boldsymbol{x})) - \text{expit}(r(18.5 \mid \text{smoking}, \text{sex}, \boldsymbol{x})). \end{aligned}$$

Other Categories (Int 1) Other studies might have used a different categorization scheme, *e.g.,* the 21 categories defined by BMI intervals for length two:

$$\leq 17, (17, 19], (19, 21], \ldots, (35, 37], > 37.$$

An individual with a BMI value between 19 and 21 thus contributes

$$\text{expit}(r(21 \mid \text{smoking}, \text{sex}, \boldsymbol{x})) - \text{expit}(r(19 \mid \text{smoking}, \text{sex}, \boldsymbol{x}))$$

to the likelihood.

Numeric Intervals (Int 2) With weight measured in kilogram and height in meters, the BMI is calculated according to its definition as BMI = weight/height^2. However, for an individual 1.75m tall weighting 76kg, all BMI values between $75.5/1.755^2 = 24.51$ and

$76.5/1.745^2 = 25.12$ are consistent with this individual due to rounding error. Thus, this individual contributes

$$\text{expit}(r(25.12 \mid \text{smoking}, \text{sex}, \boldsymbol{x})) - \text{expit}(r(24.51 \mid \text{smoking}, \text{sex}, \boldsymbol{x}))$$

to the likelihood, which automatically takes the measurement error into account. These intervals can be expected to be much larger in studies that rely on self-reported weights and heights.

Exact Measurements (Exact) If extreme precision was used to measure weight and height, BMI = weight/height^2 can be considered an "exact" observation. Because the interval around this value is very narrow, one can approximate the likelihood contribution by the density of the conditional BMI distribution

$$\frac{\partial \text{expit}(r(b \mid \text{smoking}, \text{sex}, \boldsymbol{x}))}{\partial b} \tag{5}$$

evaluated at the "exact" BMI value.

It is important to note that it is possible to evaluate the likelihood when a mixture of these different BMI measurement scales is applied to subsets of the individuals. In subject-level meta analyses, for example, it would be possible to estimate a joint model based on studies using different BMI categorizations or no categorization at all. From a purely theoretical point of view, the application of numeric intervals that take rounding error into account (Int 2) is most appropriate. The remaining three procedures must be considered approximate.

Results

Comparison of Conditional BMI Distributions

Comparison of estimated probabilities obtained from the four different likelihoods for model (4) showed that these probabilities were practically identical. For females and males of all smoking categories with baseline covariates, the estimated conditional BMI distribution evaluated at the WHO categories $b \in \{18.5, 25, 30\}$ obtained from model (4) are given in Table 1. The model was fitted to BMI observations categorized according to the WHO and to a different categorization with intervals of two BMI units (Int 1). Furthermore, numeric intervals taking rounding error into account (Int 2) and "exact" BMI values were used to estimate model (4). The approximation of the likelihood by the density was very accurate, as the estimated probabilities obtained from models estimated from numeric intervals taking rounding error into account (Int 2) and "exact" BMI values were very close. Differences occurred in the third decimal place if at all. Slightly larger differences were observed between numeric intervals (Int 2) and intervals obtained by categorization Int 1. The more extreme WHO categorization led to the largest differences in these estimated probabilities, but the results were still practically identical.

Comparison of Covariate Associations with BMI

In addition to a comparison of the estimated probabilities, we also compared the proportional log-odds ratios $\boldsymbol{\beta}$ among the four BMI likelihoods (Table 2) and did not find relevant differences. The approximation of the likelihood based on the density resulted in odds ratios

Table 1: Conditional Distribution of BMI for WHO Categories. For baseline characteristics $\boldsymbol{x}$, the probabilities obtained from model (4) for BMI ≤ 18.5, BMI ≤ 25, and BMI ≤ 30 are given for each combination of smoking and sex of the individual. The model was fitted using the likelihood (Lik) defined by BMI measurements categorized according to the WHO and according to a different categorization with intervals of two BMI units (Int 1). Numeric intervals taking rounding error into account (Int 2) and "exact" BMI values were used to estimate the model parameters. The differences between these four ways of evaluating the likelihood with respect to the estimated probabilities were marginal.

		BMI:	≤ 18.5				≤ 25				≤ 30			
Sex	Smoking	Lik.:	WHO	Int 1	Int 2	Exact	WHO	Int 1	Int 2	Exact	WHO	Int 1	Int 2	Exact
Female	Never		0.056	0.039	0.043	0.044	0.764	0.735	0.728	0.728	0.943	0.929	0.932	0.932
	Former		0.053	0.038	0.043	0.043	0.748	0.717	0.712	0.712	0.941	0.932	0.931	0.931
	Light		0.079	0.051	0.062	0.063	0.787	0.759	0.755	0.755	0.968	0.955	0.957	0.957
	Medium		0.047	0.042	0.048	0.048	0.768	0.732	0.723	0.723	0.948	0.944	0.942	0.942
	Heavy		0.084	0.086	0.071	0.071	0.740	0.705	0.713	0.712	0.946	0.937	0.938	0.939
Male	Never		0.003	0.004	0.004	0.004	0.546	0.503	0.507	0.507	0.921	0.907	0.910	0.910
	Former		0.000	0.002	0.002	0.002	0.500	0.411	0.405	0.406	0.912	0.887	0.884	0.885
	Light		0.000	0.002	0.003	0.003	0.545	0.497	0.497	0.497	0.932	0.918	0.926	0.925
	Medium		0.000	0.006	0.005	0.005	0.569	0.522	0.521	0.522	0.932	0.914	0.922	0.922
	Heavy		0.006	0.003	0.003	0.003	0.525	0.469	0.462	0.461	0.901	0.881	0.879	0.879

numerically almost identical to those obtained from numeric intervals that take the rounding error into account (Int 2). The odds ratios obtained with intervals of Int 1 differed more but were still negligible. This also applied to the marginally less accurate odds ratios obtained from models fitted to BMI values categorized according to WHO criteria. It should be noted that the lengths of the confidence intervals between the four different BMI likelihoods were in line, which indicated that not only the estimated parameters $\hat{\boldsymbol{\beta}}$ but also their estimated standard errors are comparable among the four approaches.

The large sample size led to almost all odds ratios being significant. Age was associated with a shift towards larger BMI values, while higher alcohol intake was associated with marginally reduced BMI. Lower intake of fruits and vegetables as well as less physical activity also indicated a shift to higher BMI values. The BMI distributions of people with a higher education were shifted to the left compared to those of less well-educated people. The BMI values of people of the German-speaking part of Switzerland were higher than those of the French- and Italian-speaking regions.

Impact of Smoking and Sex of the Individuals on BMI Distribution

The estimated conditional BMI distribution for all combinations of smoking and sex were clearly non-symmetric, and the impacts of smoking and sex of the individual related to changes in the mean and higher moments (Figure 1). The BMI distribution shifted towards larger BMI values from males who never smoked to male former smokers. In this case, only the mean was affected; the shape of the distribution was constant. The BMI distribution of females who never smoked and female former smokers was similar to those of males. The difference between the two sexes could not be described by a simple shift because the shapes of the two distributions clearly differed. In general, the association of smoking and BMI was less pronounced for females than for males. Compared to the associations of sex (Figure 1), the smoking associations were much smaller.

We quantified the odds ratios of the smoking association for both sexes for the BMI categories. Table 3 presents the same information as the distribution functions evaluated with the BMI categories (gray vertical lines in Figure 1) on the odds ratio scale in a condensed form. The odds of lower BMI evaluated at BMI $\in \{25, 30\}$ for male former smokers were smaller than for males who never smoked. The odds ratios for underweight and normal weight (BMI ≤ 25) and for non-obesity (BMI ≤ 30) increased for both males and females.

For current smokers, the odds ratio patterns that depended on BMI differed between males and females. All smoking levels were associated with larger odds of being underweight for females and had a U-shaped pattern. For males, this association was reversed and had an inverted U-shaped pattern. In the center of the BMI distribution (BMI ≤ 25), the odds ratios were much closer to 1 for both sexes. The odds ratios for non-obesity (BMI ≤ 30) for females indicated a trend towards smaller BMI values for current smokers. Except for heavy smokers, this effect was also found for males.

Discussion

Our study showed that it was possible to analyze and compare BMI distributions in terms of standard parameters without the need of ad hoc categorization. Continuous BMI logistic regression, which avoided ad hoc categorization of BMI values, led to deeper insights into

Table 2: Estimated Proportional Odds Ratios of Covariates. The odds ratios $\exp(\hat{\boldsymbol{\beta}})$ along with 95% confidence intervals for the covariates age (centered at 40 years), education, alcohol intake, fruit and vegetable consumption, physical activity, education, nationality, and region are given for the four ways of evaluating the likelihood of model (4), *i.e.,* , using BMI measurements categorized according to the WHO and according to a different categorization with intervals of two BMI units (Int 2), numeric intervals taking rounding error into account (Int 2), and "exact" BMI values.

	Likelihood			
Covariate	WHO	Int 1	Int 2	Exact
Age (centered at 40 in y)	0.968 0.966, 0.970	0.969 0.967, 0.971	0.968 0.967, 0.970	0.968 0.967, 0.970
Alcohol intake (g/d)	1.002 0.999, 1.004	1.003 1.001, 1.005	1.003 1.001, 1.004	1.002 1.001, 1.004
Fruit and vegetables				
High	1	1	1	1
Low	0.880 0.824, 0.940	0.928 0.874, 0.986	0.929 0.878, 0.983	0.929 0.878, 0.983
Physical activity				
High	1	1	1	1
Moderate	0.836 0.774, 0.903	0.850 0.792, 0.912	0.863 0.808, 0.921	0.862 0.808, 0.921
Low	0.695 0.640, 0.756	0.743 0.688, 0.802	0.769 0.716, 0.827	0.769 0.716, 0.826
Education				
Mandatory	1	1	1	1
Secondary	1.095 0.992, 1.209	1.252 1.141, 1.373	1.256 1.150, 1.371	1.254 1.149, 1.369
Tertiary	1.604 1.441, 1.786	1.760 1.594, 1.944	1.785 1.625, 1.961	1.781 1.622, 1.956
Nationality				
Swiss	1	1	1	1
Foreign	0.785 0.728, 0.848	0.832 0.776, 0.893	0.810 0.758, 0.864	0.809 0.758, 0.864
Region				
German speaking	1	1	1	1
French speaking	1.175 1.091, 1.266	1.147 1.071, 1.228	1.134 1.063, 1.208	1.133 1.063, 1.208
Italian speaking	1.190 1.026, 1.382	1.173 1.024, 1.344	1.236 1.086, 1.405	1.234 1.085, 1.403

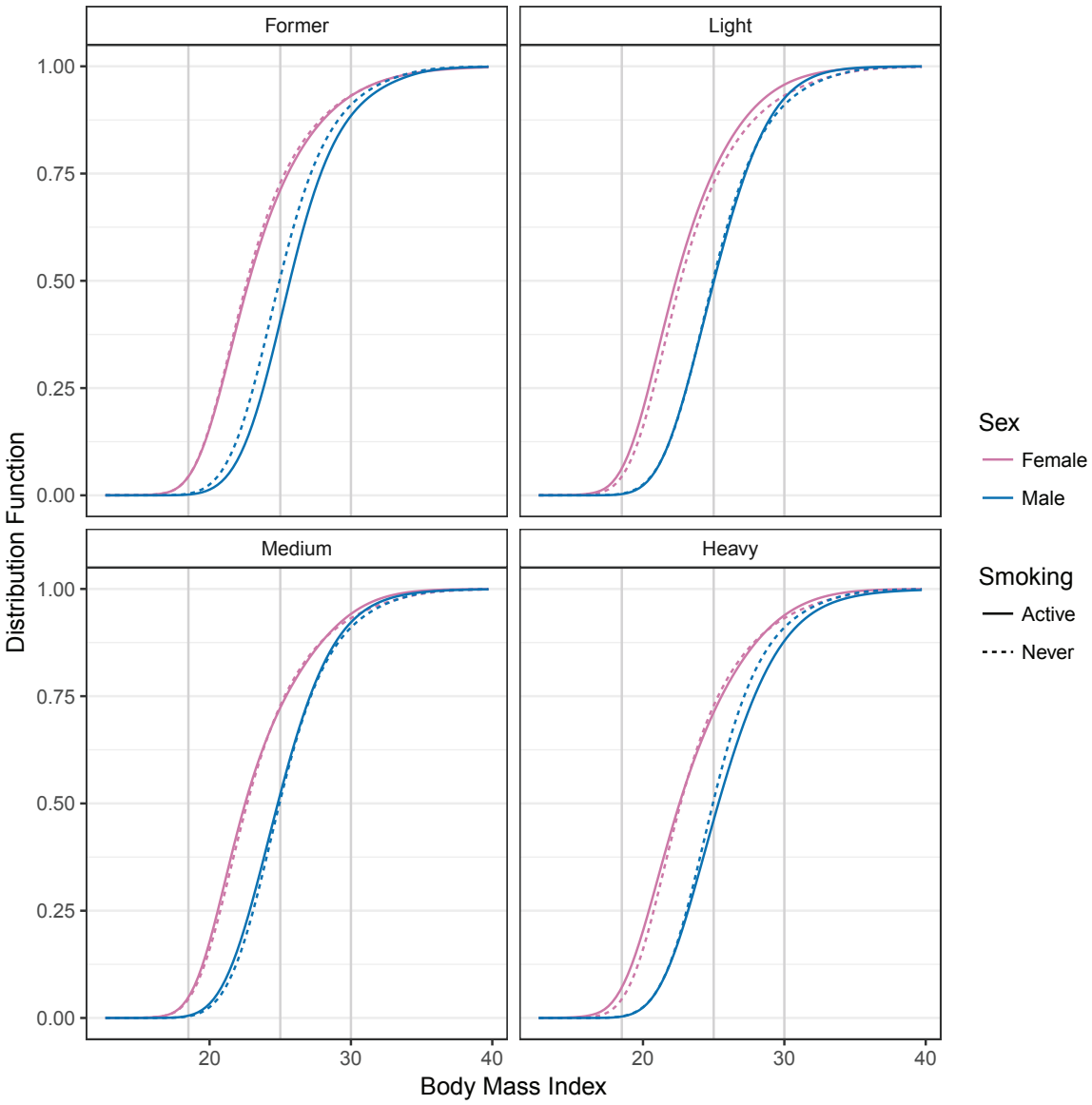

Figure 1: Conditional Distribution of BMI. For each combination of smoking and sex, the conditional distribution of BMI $\mathbb{P}(\text{BMI} \leq b \mid \text{smoking}, \text{sex}, \boldsymbol{x})$ corresponding to model (4) was evaluated for baseline covariates $\boldsymbol{x}$ at all possible BMI values b. Red, female BMI distributions; blue, male BMI distributions; solid lines, BMI distributions of active smokers; dashed lines, never smoked; gray vertical lines, WHO categories $18.5, 25, 30$. The model was fitted using "exact" BMI values.

Table 3: Estimated Non-proportional Odds Ratios for Smoking. Odds ratios comparing all levels of smoking to the level never smoked for the events BMI $\leq$ 18.5, BMI $\leq$ 25, and BMI $\leq$ 30 obtained from model (4) were fitted to "exact" BMI measurements; 95% confidence Intervals are given.

		BMI		
Sex	Smoking	$\leq$ 18.5	$\leq$ 25	$\leq$ 30
Female	Never	1	1	1
	Former	0.993 0.794, 1.241	0.922 0.825, 1.031	0.987 0.823, 1.183
	Light	1.462 1.135, 1.884	1.152 0.977, 1.358	1.638 1.187, 2.259
	Medium	1.106 0.823, 1.488	0.975 0.830, 1.146	1.182 0.894, 1.564
	Heavy	1.674 1.188, 2.358	0.925 0.756, 1.131	1.116 0.798, 1.562
Male	Never	1	1	1
	Former	0.457 0.193, 1.081	0.664 0.598, 0.737	0.757 0.649, 0.883
	Light	0.727 0.275, 1.922	0.960 0.825, 1.117	1.226 0.926, 1.622
	Medium	1.352 0.631, 2.900	1.059 0.917, 1.223	1.170 0.911, 1.503
	Heavy	0.852 0.336, 2.161	0.832 0.721, 0.961	0.716 0.579, 0.885

the impact of sex of the individuals and smoking status on the continuous BMI distribution. The model results were insensitive to BMI measurement scales or categorization schemes and matched previously reported findings on the impact of smoking and sex of the individuals on BMI. It was obvious from the conditional BMI distributions (Figure 1) that more restrictive models, *e.g.,* a conditional normal distribution with or without sex- and smoking-specific variance (Sneve and Jorde 2008), would describe the BMI distributions less accurately. The corresponding BMI-dependent odds ratios derived from continuous BMI logistic regression (Table 3) also indicated that a model that assumed proportional and thus BMI-independent odds would not be appropriate because odds ratios varied substantially as BMI cut-off points increased.

We used a parsimonious approach in defining covariate parameters. We described the impact of the covariates on the BMI distribution as being linear on the log-odds scale. We therefore assumed that the covariate parameters would be the same in all binary or polytomous logistic regression models regardless of the ad hoc categorization applied. This corresponds to the proportional odds assumption in polytomous logistic regression models. In principle, this assumption could be relaxed by allowing BMI-dependent regression coefficients $\boldsymbol{\beta}(b)$, as in multinomial regression. Similar outcome-varying parameters are called time-varying parameters in survival analysis and distribution regression in econometrics (Foresi and Peracchi 1995; Chernozhukov *et al.* 2013) and are a special case of conditional transformation models (Hothorn *et al.* 2014). Whether the models for BMI can be improved by such an approach is a matter of ongoing research.

From a practical point of view, one advantage of continuous outcome logistic regression is the possibility of evaluating the likelihood of BMI values obtained at different measurement scales or using different categorization schemes. This aspect allows the same model to be fitted, and thus allows models from studies using different BMI measurement scales to be compared. The narrower the interval representing the BMI value for a particular individual,

the more information is contributed by this individual to the likelihood. In contrast to the common procedure of downscaling all analyses by ad hoc categorization of BMI measurements to the ubiquitous WHO categories (Flegal *et al.* 2013, 2014), we propose that a post hoc categorization of model parameters and contrasts. In subject-level meta analyses, the likelihood contributions can be a mixture of exact, interval, or category-based BMI measurement scales. The likelihood can also be extended to incorporate study-specific left and right truncation when only individuals with BMI values in a pre-defined range are enrolled.

Our findings on the association between smoking and BMI are consistent with the results of previous studies. It has been shown that former smoking is associated with being overweight as well as obesity, especially for males (Chiolero *et al.* 2007; John *et al.* 2005; Mackay *et al.* 2013; Basterra-Gortari *et al.* 2010; Dare *et al.* 2015). Other studies have also observed a positive association of male heavy smokers with obesity, although the association was non-significant when male heavy smokers were compared with males who never smoked (Chiolero *et al.* 2007; John *et al.* 2005). By contrast, light and moderate smoking was associated with lower BMI values (Chiolero *et al.* 2007; John *et al.* 2005). In general, current smoking is associated with lower BMI values (Albanes *et al.* 1987; Dare *et al.* 2015; Winslow *et al.* 2015). These findings are consistent with previous findings on the effect of smoking on body weight (Audrain-McGovern and Benowitz 2011; Chiolero *et al.* 2008).

Waiving the need for ad hoc categorization and thus also for agreement on standard categories that define the parameters in models for BMI distributions makes reported scientific results less dependent on these standard categories, and most importantly, less dependent on the WHO criteria. Considering that BMI distributions are subject to change at the population level over time (Ng *et al.* 2014), insistence on the application of standards defined decades ago leads to an increasing discrepancy between models and data. Continuous BMI logistic regression is an attempt to narrow this gap.

Online Appendix: Computational Details

The intercept functions $\alpha(b)_{\text{smoking:sex}}$ for each combination of smoking and sex were estimated as smooth and monotonically increasing functions of b. The constraints $\text{expit}(r(\infty \mid \text{smoking}, \text{sex}, \boldsymbol{x})) = 1$ and $\text{expit}(r(0 \mid \text{smoking}, \text{sex}, \boldsymbol{x})) = 0$ restrict the BMI distribution on the positive numbers. For each of the ten strata given by the five smoking categories and two categories of sex, an intercept function was defined by six increasing parameters of a Bernstein polynomial (Farouki 2012) of order five. This choice ensures smoothness and monotonicity and allows flexible intercept functions and thus regression functions r and conditional BMI distributions to be described by model (4). The monotonicity constrained on the intercept functions renders the addition of smoothing penalty terms to the likelihood unnecessary, and simple maximum-likelihood estimation was performed for all model parameters simultaneously. When the likelihood was evaluated for BMI values in WHO categories, the sex- and smoking-specific intercept function was parameterized in terms of the step-function $\alpha(b)$ (see Formula (3)) defined for the proportional odds model. All computations were performed using R version 3.3.3 (R Core Team 2015). The **mlt** package (Hothorn 2017, 2016) was used to estimate continuous outcome logistic regression models. The underlying statistical theory is described in Hothorn *et al.* (2016).

A blueprint for the estimation of conditional BMI logistic regression using the **mlt** package in

R, assuming the data are available in a data frame `sgb` with variables `bmi` (the numeric BMI values), `smoking`, and `sex` (smoking and sex as factors), as well as `age` and `alcohol` (numeric age and alcohol intake) with optional sampling weights `weights`, is

```
### attach mlt package
library("mlt")
### compute support of BMI distribution
bmis <- quantile(sgb$bmi, prob = c(.01, .99), na.rm = TRUE)
vBMI <- numeric_var("bmi", bounds = c(0, Inf),
    support = bmis, add = c(-5, 5))
### set-up increasing Bernstein polynomial
bBMI <- Bernstein_basis(vBMI, order = 5, ui = "increasing")
### set-up dummy encodings for smoking and sex
bSMK <- as.basis(~ smoking - 1, data = sgb)
bSEX <- as.basis(~ sex - 1, data = sgb)
### specify the model with strata sex and smoking and
### covariates age and alcohol
mod <- ctm(bBMI, interacting = b(sm = bSMK, sex = bSEX),
           shifting = ~ age + alcohol, data = sgb,
           todistr = "Logistic")
### fit model to data with weighted `exact' likelihood
fmod <- mlt(mod, data = sgb, scale = TRUE,
            weights = sgb$weights)
### plot conditional BMI distribution for 18 year-old
### never-smoking non-drinking female
nsf18 <- data.frame(sex = factor(c("Female", "Male"))[1],
    smoking = factor(c("Never", "Former", "Light", "Medium",
                       "Heavy"))[1],
    age = 18, alcohol = 0)
plot(fmod, newdata = nsf18, type = "distribution")
```

Continuous outcome logistic regression, as a model for a continuous conditional distribution implemented in **mlt**, has a very strong connection to the Cox proportional hazards model, which describes the conditional continuous distribution of a survival time outcome with fully parameterized log-cumulative hazard function (Hothorn *et al.* 2016; Hothorn 2016). A Cox model for the conditional BMI distribution could be written as (Doksum and Gasko 1990)

$$\text{cloglog}(\mathbb{P}(\text{BMI} \leq b \mid \text{smoking}, \text{sex}, \boldsymbol{x})) = r(b \mid \text{smoking}, \text{sex}, \boldsymbol{x}).$$

In this case, the logistic link in (1) was replaced by the complementary log-log link. In the absence of covariates $\boldsymbol{x}$, the results obtained from our continuous BMI logistic regression model and a Cox model stratified by sex and smoking would not be affected by this change, because for each combination of sex and smoking, a corresponding equivalent intercept function $\alpha(b)_{\text{smoking:sex}}$ (the sex- and smoking-specific log-cumulative hazard in the stratified Cox model) can be found on both the logit and cloglog scales. However, the interpretation of $\boldsymbol{\beta}$ changes from proportional log-odds ratios to proportional log-hazard ratios. In contrast to the partial likelihood of Cox models that treat the intercept functions as nuisance parameters,

the likelihood for continuous outcome logistic regression is evaluated for fully parameterized intercept functions and all model parameters are estimated by maximum likelihood (similar to McLain and Ghosh 2013). The corresponding monotonicity constraint allows smooth conditional distribution functions to be estimated without adding smoothing parameters to the likelihood (Hothorn *et al.* 2016; Hothorn 2016).

References

Agresti A (2013). *Categorical Data Analysis*. John Wiley & Sons, Hoboken, New Jersey, 3rd edition.

Albanes D, Jones DY, Micozzi MS, Mattson ME (1987). "Associations Between Smoking and Body Weight in the US Population: Analysis of NHANES II." *American Journal of Public Health*, **77**(4), 439–44.

Altman DG, Royston P (2004). "The Cost of Dichotomising Continuous Variables." *British Medical Journal*, **332**(7549), 1080. doi:10.1136/bmj.332.7549.1080.

Audrain-McGovern J, Benowitz NL (2011). "Cigarette Smoking, Nicotine, and Body Weight." *Clinical Pharmacology & Therapeutics*, **90**(1), 164–168. doi:10.1038/clpt.2011.10.

Basterra-Gortari FJ, Forga L, Bes-Rastrollo M, Toledo E, Martínez JA, Martínez-González MA (2010). "Effect of Smoking on Body Weight: Longitudinal Analysis of the SUN Cohort." *Revista Española de Cardiología (English Edition)*, **63**(1), 20–27. doi:10.1016/S1885-5857(10)70005-0.

Bundesamt für Statistik (2013). *Die Schweizerische Gesundheitsbefragung 2012 in Kürze – Konzept, Methode, Durchführung*. Bern. URL http://www.bfs.admin.ch.

Chang VW, Christakis NA (2003). "Self-perception of Weight Appropriateness in the United States." *American Journal of Preventive Medicine*, **24**(4), 332–339. doi:10.1016/S0749-3797(03)00020-5.

Chernozhukov V, Fernández-Val I, Melly B (2013). "Inference on Counterfactual Distributions." *Econometrica*, **81**(6), 2205–2268. doi:10.3982/ECTA10582.

Chiolero A, Faeh D, Paccaud F, Cornuz J (2008). "Consequences of Smoking for Body Weight, Body Fat Distribution, and Insulin Resistance." *The American Journal of Clinical Nutrition*, **87**, 801–809.

Chiolero A, Jacot-Sadowski I, Faeh D, Paccaud F, Cornuz J (2007). "Association of Cigarettes Smoked Daily With Obesity in a General Adult Population." *Obesity*, **15**(5), 1311–1318. doi:10.1038/oby.2007.153.

Clair C, Chiolero A, Faeh D, Cornuz J, Marques-Vidal P, Paccaud F, Mooser V, Waeber G, Vollenweider P (2011). "Dose-dependent Positive Association Between Cigarette Smoking, Abdominal Obesity and Body Fat: Cross-sectional Data From a Population-based Survey." *BMC Public Health*, **11**, 23. doi:10.1186/1471-2458-11-23.

Dare S, Mackay DF, Pell JP (2015). "Relationship Between Smoking and Obesity: a Cross-sectional Study of 499,504 Middle-aged Adults in the UK General Population." *PloS ONE*, **10**(4), e0123579. doi:10.1371/journal.pone.0123579.

Doksum KA, Gasko M (1990). "On a Correspondence Between Models in Binary Regression Analysis and in Survival Analysis." *International Statistical Review*, **58**(3), 243–252.

Farouki RT (2012). "The Bernstein Polynomial Basis: A Centennial Retrospective." *Computer Aided Geometric Design*, **29**(6), 379–419. doi:10.1016/j.cagd.2012.03.001.

Flegal KM, Kit BK, Graubard BI (2014). "Body Mass Index Categories in Observational Studies of Weight and Risk of Death." *American Journal of Epidemiology*, **180**(3), 288–296. doi:10.1093/aje/kwu111.

Flegal KM, Kit BK, Orpana H, Graubard BI (2013). "Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories: A Systematic Review and Meta-analysis." *Journal of the American Medical Association*, **309**(1), 71–82. doi:10.1001/jama.2012.113905.

Foresi S, Peracchi F (1995). "The Conditional Distribution of Excess Returns: An Empirical Analysis." *Journal of the American Statistical Association*, **90**(430), 451–466. doi:10.1080/01621459.1995.10476537.

Hothorn T (2016). *Most Likely Transformations: The mlt Package*. R package vignette version 0.1-4, URL https://CRAN.R-project.org/package=mlt.docreg.

Hothorn T (2017). *mlt: Most Likely Transformations*. R package version 0.1-3, URL https://CRAN.R-project.org/package=mlt.

Hothorn T, Kneib T, Bühlmann P (2014). "Conditional Transformation Models." *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, **76**(1), 3–27. doi:10.1111/rssb.12017.

Hothorn T, Möst L, Bühlmann P (2016). "Most Likely Transformations." *Technical report*, arXiv 1508.06749, v2. URL https://arxiv.org/abs/1508.06749.

John U, Hanke M, Rumpf HJ, Thyrian JR (2005). "Smoking Status, Cigarettes Per Day, and Their Relationship to Overweight and Obesity Among Former and Current Smokers in a National Adult General Population Sample." *International Journal of Obesity*, **29**(10), 1289–1294. doi:10.1038/sj.ijo.0803028.

Lindsey JK (1996). *Parametric Statistical Inference*. Clarendon Press, Oxford, UK.

Mackay DF, Gray L, Pell JP (2013). "Impact of Smoking and Smoking Cessation on Overweight and Obesity: Scotland-wide, Cross-sectional Study on 40,036 Participants." *BMC Public Health*, **13**, 348. doi:10.1186/1471-2458-13-348.

McLain AC, Ghosh SK (2013). "Efficient Sieve Maximum Likelihood Estimation of Time-Transformation Models." *Journal of Statistical Theory and Practice*, **7**(2), 285–303.

Mead E, Batterham AM, Atkinson G, Ells LJ (2016). "Predicting Future Weight Status From Measurements Made in Early Childhood: a Novel Longitudinal Approach Applied to Millennium Cohort Study Data." *Nutrition & Diabetes*, **6**(3), e200. doi:10.1038/nutd.2016.3.

Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NME, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwari P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DFJ, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SEAH, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KMV, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJC, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJL, Gakidou E (2014). "Global, Regional, and National Prevalence of Overweight and Obesity in Children and Adults During 1980–2013: a Systematic Analysis for the Global Burden of Disease Study 2013." *The Lancet*, **384**(9945), 766–781. doi:10.1016/S0140-6736(14)60460-8.

R Core Team (2015). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Sneve M, Jorde R (2008). "Cross-sectional Study on the Relationship Between Body Mass Index and Smoking, and Longitudinal Changes in Body Mass Index in Relation to Change in Smoking Status: the Tromso Study." *Scandinavian Journal of Public Health*, **36**(4), 397–407. doi:10.1177/1403494807088453.

UNESCO Institute for Statistics (2012). *International Standard Classification of Education – ISCED 2011*. Montreal. URL http://www.uis.unesco.org/Education/Documents/isced-2011-en.pdf.

Wells JCK, Fewtrell MS (2006). "Measuring Body Composition." *Archives of Disease in Childhood*, **91**(7), 612–617. doi:10.1136/adc.2005.085522.

Winslow UC, Rode L, Nordestgaard BG (2015). "High Tobacco Consumption Lowers Body Weight: A Mendelian Randomization Study of the Copenhagen General Population Study." *International Journal of Epidemiology*, **44**(2), 540–550. doi:10.1093/ije/dyu276.

World Health Organization (2000). *Obesity: Preventing and Managing the Global Epidemic*. Geneva. WHO Technical Report Series 894, URL http://whqlibdoc.who.int/trs/WHO_TRS_894.pdf.

World Health Organization (2003). *Fruit and Vegetable Promotion Initiative*. Geneva. URL http://www.who.int/hpr/NPH/fruit_and_vegetables/fruit_and_vegetable_report.pdf.

Affiliation:

Tina Lohse, Sabine Rohrmann, David Faeh, Torsten Hothorn
Institut für Epidemiologie, Biostatistik und Prävention
Universität Zürich
Hirschengraben 84, CH-8001 Zürich, Switzerland
`Torsten.Hothorn@uzh.ch`

Paper IV

Type A personality and mortality: Competitiveness but not speed is associated with increased risk

Tina Lohse, Sabine Rohrmann, Aline Richard, Matthias Bopp, David Faeh for the Swiss National Cohort Study Group

Published in Atherosclerosis. 2017. 262:19-24.

Atherosclerosis 262 (2017) 19–24

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Type A personality and mortality: Competitiveness but not speed is associated with increased risk

Tina Lohse [a], Sabine Rohrmann [a], Aline Richard [a], Matthias Bopp [a], David Faeh [a, b, *], for the Swiss National Cohort Study Group

[a] Division of Chronic Disease Epidemiology, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland
[b] Health Division – Nutrition and Dietetics, Bern University of Applied Sciences, Bern, Switzerland

ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form
22 March 2017
Accepted 20 April 2017
Available online 22 April 2017

Keywords:
Type A personality
Mortality
Bortner scale
Cardiovascular disease (CVD)
Competitiveness
Speed

ABSTRACT

Background and aims: Type A behavior pattern (TABP) is a possible risk factor for cardiovascular disease (CVD). However, existing evidence is conflicting, also because studies did not examine underlying traits separately. In this study, we investigated whether all-cause and CVD mortality were associated with the Bortner Scale, a measure of TABP, in particular with its subscales competitiveness and speed.
Methods: Information on Bortner Scale and covariates of 9921 participants was collected at baseline in two cross-sectional studies that were linked with mortality information, yielding a follow-up of up to 37 years. We analyzed the Bortner Scale and its two subscales competitiveness and speed. Applying Cox regression models, we investigated the association with all-cause, CVD, and specific CVD type mortality.
Results: During follow-up, 3469 deaths were observed (1118 CVD deaths). The total Bortner Scale was not associated with mortality, only its subscales. In women, competitiveness was positively associated with all-cause mortality (highest category *vs.* the lowest, HR 1.25 [95% CI 1.08,1.44]), CVD mortality (1.39 [1.07,1.81]), and ischemic heart disease mortality (intermediate category *vs.* the lowest, 1.46 [1.02,2.10]). In men, CVD mortality was inversely associated with speed (highest category *vs.* the lowest, 0.74 [0.59,0.93]).
Conclusions: The subscales of the Bortner Scale may be associated with CVD in an opposed manner and may therefore have to be analyzed separately. More studies are needed to further investigate this association, also considering differences by sex. Persons scoring high in the competitiveness subscale ought to be screened and counselled in order to reduce their CVD risk.

1. Introduction

The concept of Type A behavior pattern (TABP) was introduced in the 1970s. Individuals having this trait are assumed to have a higher risk for cardiovascular disease (CVD) [1]. TABP is defined as an action-emotion complex in which an individual's behavior is characterized by ambitiousness, competitiveness, easily aroused hostility, impatience and an exaggerated sense of time urgency [1].

Early investigations of the association between TABP and CVD indicated a positive relationship with CVD incidence [2–6]. Furthermore, it was shown that the clinical outcome of CHD was improved in patients undergoing behavioral counseling [7,8]. However, subsequent studies on CVD incidence [9–11] and mortality [12–14] showed conflicting results. No associations of TABP with cancer risk were observed [15,16].

Various instruments for measuring TABP were used to investigate its association with health outcomes. As the concept of TABP includes many different aspects of personality, it is a challenge to capture it comprehensively. The Bortner Scale is a frequently used instrument. Edwards et al. (1990) performed an exploratory factor analysis and a subsequent confirmatory analysis of dimensionality to show that the Bortner Scale captures mainly two components of TABP: competitiveness and speed [17]. The assignment of the Bortner Scale items to these two subscales was driven by the aim to maintain a simple structure and to enhance interpretability. In fact, the subscales of the Bortner Scale may be differently associated with morbidity and mortality and thus the effect estimates can be underestimated towards the null, when analyzing the subscales

* Corresponding author. Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich, Hirschengraben 84, 8001 Zürich, Switzerland.
E-mail address: david.faeh@uzh.ch (D. Faeh).

http://dx.doi.org/10.1016/j.atherosclerosis.2017.04.016
0021-9150/

only jointly. Hence, an analysis on subscale level is recommended [17]. To our knowledge, other studies did not consider this approach.

In this study, we investigated whether all-cause, CVD, CVD-specific (i.e. ischemic heart disease and cerebrovascular disease), and cancer mortality were associated with the Bortner Scale and its two subscales competitiveness and speed.

2. Materials and methods

2.1. Study design, setting, and participants

We used data of two population-based Swiss studies, the first of three waves of MONICA (MONItoring of trends and determinants in CArdiovscular disease) and the NRP1A (National Research Program 1A, community-based primary prevention of cardiovascular disease). In order to establish a mortality follow-up, the study cohorts were linked with the Swiss National Cohort (SNC) using a record linkage procedure. The study participants were aged ≥18 years at baseline.

The first wave of the MONICA study was conducted in 1983 and was part of an international multicenter study initiated by the World Health Organization [18]. The NRP1A study was conducted from 1977 to 1979 [19]. In both studies, a self-administered questionnaire and a health examination were included at baseline. Information on the cause of death was obtained through the SNC using underlying cause of death from the national death registry until 2014 [20,21]. The SNC is a national longitudinal research platform linking census records with Federal death and migration records covering all residents of Switzerland. Details about the linkage process were reported elsewhere [20]. Successful linkage was possible for 97% participants of the MONICA study and 94% of the NRP1A study [21,22]. Approval for the SNC and the linkage with MONICA and NRP1A was obtained from the Ethics Committee of the Canton of Zurich (KEK Zurich, KEK-StV No. 13/06 and amendment of June 12, 2008).

2.2. Variables

We used the Bortner Scale as a measure of TABP, consisting of 13 items. Compared with the original scale, the item „no outside interests“ was not included. According to Edwards et al. (1990), we built the two subscales of speed (9 items: never late, rushed, impatient, goes all out, doing lots at once, forceful, wants job recognized, fast, hide feelings) and competitiveness (3 items: competitive, hard driving, ambitious) [17]. The Bortner Scale additionally included the item “anticipate”. Each item ranges between 0 and 5, with 5 corresponding to TABP. Age, education, marital status, nationality, language region, study, smoking status, blood pressure, Body Mass Index (BMI), physical activity, and alcohol consumption were considered as potential confounders.

Causes of death were coded according to the International Classification of Diseases (ICD; 8th revision until 1994, 10th revision since 1995). We investigated all-cause, CVD (ICD-8: 410–458, ICD-10: I20-I99), CVD-specific (cerebrovascular diseases [ICD-8: 430–38, ICD-10: I60-69], ischemic heart disease [ICD-8: 410–414, ICD-10: I20-25]), and total cancer (ICD-8140–209, 225, 230–239; ICD-10: C00-C97, D32-D33, D37-D48) mortality.

2.3. Data sources and assessment

Data on the Bortner Scale and potential confounders were assessed by self-administered questionnaires [18,19]. Height and weight, which were used to calculate the covariate BMI and blood pressure were measured at baseline [23].

2.4. Statistical methods

We pooled the data of MONICA and NRP1A as data collection on the variables of interest was comparable. We added a variable indicating the study, i.e. MONICA or NRP1A, to all models.

Cox regression was performed for all-cause, CVD, specific CVD type (ischemic heart disease, cerebrovascular disease), and cancer mortality. For the Cox regression, the Bortner Scale and its subscales were categorized. Therefore, we built 3 groups by taking the 25th and the 75th percentile as cut-off points (total scale: ≤35, 36 to 44, ≥45, competitiveness subscale: ≤6, 7 to 9, ≥10, speed subscale: ≤26, 27 to 33, ≥34). As sex differences were neglectable, we used similar cut-off points for men and women. The 25th percentile was used as reference category in the categorical model. A priori, we decided to stratify by sex. Cox regression models were adjusted for age, education, nationality, marital status, language region, and study (MONICA wave 1, NRP1A) in the basic model as well as smoking status, physical activity, alcohol consumption, BMI, and blood pressure in the full model. Age was included as continuous variable; education as the highest degree obtained and was categorized into mandatory, secondary, and tertiary. Nationality was included as being Swiss or foreign. Marital status comprised of the categories: single, married, widowed, and divorced/separated. Language region reflects cultural differences within Switzerland and the categories German/Romansh, French, and Italian were taken into account. Smoking status was categorized into never, former, light (1–9 cigarettes per day), moderate (10–19), and heavy (>19). We categorized BMI (kg/m^2) into underweight <18.5, normal-weight ≥18.5 - <25, overweight ≥25 - <30, and obesity ≥30 [24]. Physical activity during leisure was included as sedentary, moderate, and high. Alcohol consumption was categorized into consumption yesterday yes or no. Observations with missing values on covariates were kept in the Cox regression by adding a missing category to each variable.

In a sensitivity analysis, we investigated whether using a competing-risks regression instead of a Cox regression model for the CVD-specific mortality, i.e. ischemic heart disease and cerebrovascular diseases, would have changed the results. Furthermore, for statistically significant associations observed in the Cox regression analysis, we checked for interactions with lifestyle and sociodemographic variables. All analyses were performed using STATA 13.1, College Station, TX, USA.

3. Results

Our analyses included 4839 men and 5082 women (Table 1). Men were more likely to be overweight or obese (50.3% *vs.* 29.8%), smoker (44.4% *vs.* 26.2%), and having consumed alcohol yesterday (71.3% *vs.* 41.4%); on the other hand they were more likely to have a high level of physical activity during leisure (14.9% *vs.* 4.0%) and being educated on a tertiary level (University, 7.7% *vs.* 2.1%). Hypertension (BP ≥ 140/90 mmHg) was prevalent in 24.6% of men and 27.3% of women. Lifestyle and socioeconomic factors also differed by TABP (data not shown). The more distinct TABP was, the less likely were never smoking and physical activity. On the other hand alcohol intake, being of foreign nationality and having a higher educational degree was more likely in TABP prone individuals.

In total, 3469 deaths occurred, of which 1118 were due to CVD and 1117 to cancer (Table 2); 464 deaths were caused by ischemic heart disease and 229 by cerebrovascular diseases. Median survival was 29.8 years.

The distribution of the Bortner Scale (median of 41) and of its subscales competitiveness (median of 8) and speed (median of 30) is shown in Fig. 1. We did not observe an association between total Bortner Scale and mortality, but with its subscales (Table 2). A

Table 1
Characteristics of the study population by sex (marital status and language region not shown).[a]

	Men		Women	
Age (y)	43.4 ± 13.7		43.7 ± 14.3	
Survival (y)	27.3 ± 10.0		29.5 ± 8.8	
Bortner Scale[b]	40.8 ± 7.4		40.3 ± 7.2	
Competitiveness subscale[b]	8.3 ± 2.7		7.7 ± 2.5	
Speed subscale[b]	30.2 ± 5.6		30.3 ± 5.6	
Total	4839	100.0	5082	100.0
Education				
Tertiary	374	7.7	108	2.1
Secondary	3068	63.4	2838	55.8
Mandatory	1394	28.8	2133	42.0
Missing	3	0.1	3	0.1
Nationality				
Swiss	3907	80.7	4298	84.6
Foreign	932	19.3	784	15.4
Study[c]				
MONICA I	1514	31.3	1393	27.4
NRP1A	3325	68.7	3689	72.6
Smoking[d]				
Never	1509	31.2	3144	61.9
Former	1038	21.4	438	8.6
Light	575	11.9	415	8.2
Moderate	509	10.5	450	8.8
Heavy	1065	22.0	466	9.2
Missing	143	3.0	169	3.3
Physical activity[e]				
Sedentary	1284	26.5	1494	29.4
Moderate	2777	57.4	3279	64.5
High	722	14.9	204	4.0
Missing	56	1.2	105	2.1
Alcohol intake, yesterday				
Yes	3448	71.3	2103	41.4
No	1342	27.7	2906	57.2
Missing	49	1.0	73	1.4
BMI				
Normal-weight	2363	48.8	3322	65.4
Underweight	39	0.8	240	4.7
Overweight	1977	40.9	1139	22.4
Obese	455	9.4	376	7.4
Missing	5	0.1	5	0.1
Blood pressure[f]				
Normal, hypotension	1131	23.4	2112	41.6
Prehypertension	2503	51.8	2036	40.0
Grade 1	897	18.5	649	21.8
Grade 2	195	4.0	186	3.6
Grade 3	103	2.1	96	1.9
Missing	10	0.2	3	0.1

[a] Values are means ± SDs or n and %.
[b] Categorization: total scale: ≤35, 36 to 44, ≥45, competitiveness subscale: ≤6, 7 to 9, ≥10, speed subscale: ≤26, 27 to 33, ≥34.
[c] Study: MONICA (MONItoring of trends and determinants in CArdiovascular disease), NRP1A (National Research Program 1A).
[d] Smoking: never, former, light (1–9 cigarettes per day), moderate (10–19), and heavy (>19).
[e] Physical activity during leisure, including sports: sedentary (e.g. TV, reading), moderate (e.g. walking, cycling, gardening), high (e.g. soccer, natation, rowing).
[f] Blood pressure: normal, hypotension (mean systolic <120 mmHg, mean diastolic <80 mmHg), prehypertension (120–139 mmHg, 80–89 mmHg), Grade 1 (140–159 mmHg, 90–99 mmHg), Grade 2 (160–179 mmHg, 100–109 mmHg), Grade 3 (>179 mmHg, >109 mmHg).

positive association of competitiveness with all-cause mortality was observed in women (full model, comparing the highest category with the lowest, HR 1.25 [95% CI 1.08,1.44]). Speed was inversely associated with CVD mortality in men (0.74 [0.59,0.93]), whereas competitiveness was positively associated with CVD mortality in women (1.39 [1.07,1.81]).

Competitiveness was positively associated with ischemic heart disease mortality in women (full model, comparing the intermediate category with the lowest, 1.46 [1.02,2.10]). The effect estimates were about the same for the basic and the full model (lifestyle factor adjusted).

The sensitivity analysis on competing risks for CVD specific mortality led to similar results with regard to significance for ischemic heart disease (data not shown). In men, for cerebrovascular diseases the non-significant result of the Cox regression became statistically significant on the competitiveness subscale (full model, comparing the highest category with the lowest, 1.87 [1.01,3.45]). Interactions of the subscales competitiveness and speed with lifestyle variables were statistically non-significant (data not shown). For the association between all-cause mortality and the competitiveness subscale, significant interactions were observed with sex ($p = 0.010$) and education ($p=0.007$); but not for CVD mortality (data not shown).

4. Discussion

In our study, the Bortner Scale as a measure of TABP was not associated with all-cause or cause-specific mortality. However, several associations were found for its subscales such that, competitiveness was positively associated with all-cause, CVD, and ischemic heart disease mortality in women and speed was inversely associated with CVD mortality in men. Adjusting for lifestyle and clinical factors did not substantially change the results.

Studies on the association between health outcomes and TABP as well as personality in general showed conflicting results. Consistent with our null for the Bortner Scale, other studies also showed no association between TABP and mortality. This was observed for all-cause, CVD, and cancer mortality [9,14,25]. In contrast to these studies, we separately analyzed the subscales competitiveness and speed of the Bortner Scale. This approach revealed the importance of competitiveness in women and speed in men.

TABP and its associations with CVD as well as cancer incidence were also investigated by others. While early investigations reported positive associations for CVD outcomes [2–6], most studies failed to reproduce these findings including a meta-analysis of prospective studies on coronary heart disease [10,11,26–29]. Gallacher et al. examined the role of length of follow-up and showed that high scores of the Bortner Scale were associated with higher risk for coronary heart disease events within the first 5 years of follow-up only. Based on this finding, the authors suggested that TABP increases the exposure to potential triggers, i.e. circumstances inducing extreme cardiovascular activity, and is not directly affecting the process of atherosclerosis [30]. In line with our results, cancer incidence was not associated with TABP [15].

Studies investigating personality traits in general observed for all-cause mortality an association with conscientiousness only [31–33]. For CVD mortality, there was evidence for a positive association with neuroticism [12,34], anger, and hostility [35]. Furthermore, in a pooled analysis, a positive association was shown between extraversion and stroke mortality as well as an inverse association between conscientiousness and both coronary heart disease and stroke mortality [12]. An earlier study by Nakaya et al. did not show an association of personality with ischemic heart disease or stroke deaths [36]. Although we did not find an interaction between the subscales of the Bortner Scale and education for CVD mortality, a growing body of evidence suggests that the association between psychological factors and CVD risk might depend on socioeconomic status [37,38]. In line with our results, for cancer incidence as well as mortality no association with personality was observed [16,39].

Most of the studies reported their findings for men and women combined. Only few studies restricting to males [6,10,26,27,33] or females [32] presented sex-specific figures, however without finding significant associations. The sex-specific results in the

Table 2
Association between mortality and Bortner Scale, and its subscales competitiveness and speed. HR (95% CI), statistically significant results are highlighted in bold.

Mortality	Basic model[a]			Full model[b]	
	1[c,d]	2	3	2	3
All-cause					
Men cases, n[e]	529	848	526		
Bortner Scale	1	0.97 (0.87; 1.08)	0.95 (0.84; 1.08)	0.97 (0.87; 1.09)	0.94 (0.83; 1.07)
Competitiveness	1	1.00 (0.90; 1.11)	0.95 (0.84; 1.08)	1.01 (0.91; 1.13)	0.96 (0.85; 1.09)
Speed	1	0.94 (0.85; 1.05)	0.94 (0.83; 1.07)	0.92 (0.83; 1.03)	0.90 (0.79; 1.02)
Women cases, n	463	736	367		
Bortner Scale	1	0.98 (0.87; 1.11)	1.13 (0.98; 1.30)	1.02 (0.91; 1.15)	1.15 (1.00; 1.33)
Competitiveness	1	1.07 (0.96; 1.20)	**1.26 (1.09;1.45)**	1.08 (0.96; 1.21)	**1.25 (1.08;1.44)**
Speed	1	0.95 (0.85; 1.06)	1.05 (0.91; 1.20)	0.97 (0.87; 1.09)	1.05 (0.92; 1.21)
CVD					
Men cases, n	205	274	152		
Bortner Scale	1	0.87 (0.73; 1.05)	0.83 (0.67; 1.03)	0.89 (0.74; 1.07)	0.84 (0.68; 1.05)
Competitiveness	1	1.06 (0.88; 1.27)	0.90 (0.72; 1.12)	1.07 (0.89; 1.29)	0.92 (0.73; 1.15)
Speed	1	0.89 (0.75; 1.07)	**0.77 (0.62;0.97)**	0.86 (0.72; 1.03)	**0.74 (0.59;0.93)**
Women cases, n	161	236	90		
Bortner Scale	1	1.05 (0.85; 1.28)	1.04 (0.80; 1.36)	1.14 (0.92; 1.40)	1.14 (0.86; 1.49)
Competitiveness	1	**1.26 (1.04;1.54)**	**1.35 (1.04;1.75)**	**1.30 (1.06;1.59)**	**1.39 (1.07;1.81)**
Speed	1	1.01 (0.83; 1.23)	1.01 (0.78; 1.31)	1.07 (0.88; 1.30)	1.06 (0.81; 1.38)
Ischemic heart disease					
Men cases, n	100	129	75		
Bortner Scale	1	0.82 (0.63; 1.07)	0.81 (0.60; 1.11)	0.84 (0.64; 1.10)	0.83 (0.61; 1.13)
Competitiveness	1	1.09 (0.84; 1.41)	0.77 (0.55; 1.08)	1.13 (0.87; 1.47)	0.81 (0.58; 1.14)
Speed	1	0.87 (0.67; 1.13)	0.85 (0.62; 1.17)	0.83 (0.64; 1.07)	0.82 (0.60; 1.13)
Women cases, n	53	80	27		
Bortner Scale	1	1.03 (0.72; 1.47)	0.92 (0.57; 1.48)	1.14 (0.80; 1.64)	1.04 (0.64; 1.69)
Competitiveness	1	1.39 (0.97; 1.99)	1.46 (0.92; 2.33)	**1.46 (1.02;2.10)**	1.55 (0.97; 2.47)
Speed	1	0.75 (0.54; 1.06)	0.91 (0.59; 1.42)	0.81 (0.57; 1.14)	0.98 (0.63; 1.54)
Cerebrovascular diseases					
Men cases, n	31	48	22		
Bortner Scale	1	0.99 (0.63; 1.56)	0.79 (0.45; 1.38)	1.10 (0.69; 1.76)	0.89 (0.50; 1.60)
Competitiveness	1	1.35 (0.83; 2.21)	1.44 (0.82; 2.50)	1.45 (0.88; 2.37)	1.62 (0.92; 2.86)
Speed	1	1.03 (0.66; 1.62)	0.71 (0.38; 1.30)	1.05 (0.66; 1.65)	0.69 (0.37; 1.28)
Women cases, n	44	59	25		
Bortner Scale	1	0.88 (0.59; 1.31)	0.93 (0.56; 1.54)	0.93 (0.62; 1.39)	1.01 (0.60; 1.69)
Competitiveness	1	1.20 (0.81; 1.76)	1.16 (0.69; 1.95)	1.26 (0.85; 1.87)	1.17 (0.70; 1.98)
Speed	1	1.22 (0.83; 1.79)	0.91 (0.53; 1.55)	1.26 (0.85; 1.86)	0.95 (0.56; 1.64)
Cancer					
Men cases, n	155	301	183		
Bortner Scale	1	1.12 (0.92; 1.37)	1.01 (0.81; 1.25)	1.12 (0.92; 1.36)	0.97 (0.78; 1.21)
Competitiveness	1	1.02 (0.84; 1.23)	0.99 (0.80; 1.23)	1.02 (0.84; 1.23)	0.99 (0.80; 1.23)
Speed	1	1.03 (0.85; 1.25)	0.96 (0.76; 1.19)	1.02 (0.84; 1.23)	0.90 (0.72; 1.12)
Women cases, n	130	216	132		
Bortner Scale	1	0.93 (0.74; 1.16)	1.14 (0.89; 1.46)	0.96 (0.77; 1.20)	1.14 (0.89; 1.47)

Table 2 (*continued*)

Mortality	Basic model[a]			Full model[b]	
	1[c,d]	2	3	2	3
Competitiveness	1	1.05 (0.85; 1.29)	1.23 (0.95; 1.59)	1.05 (0.85; 1.29)	1.20 (0.93; 1.56)
Speed	1	0.89 (0.72; 1.10)	1.00 (0.79; 1.28)	0.91 (0.74; 1.13)	0.99 (0.78; 1.27)

[a] Basic model adjusted for age, study, marital status, language region, education, and nationality.
[b] Full model additionally adjusted for smoking status, BMI category, physical activity, alcohol consumption, and systolic blood pressure.
[c] Reference category.
[d] Categorization: total scale: ≤35, 36 to 44, ≥45, competitiveness subscale: ≤6, 7 to 9, ≥10, speed subscale: ≤26, 27 to 33, ≥34.
[e] Cases (n) for the Bortner Scale, identical for the basic and the full model.

competitiveness subscale that we found might be partly explained by a greater likelihood of CVD events induced by postmenopausal hormone replacement therapy [40]. The inconsistent results for TABP as well as personality in general might be due to different exposure definitions and measurement instruments. In the context of Type D personality (i.e. the general tendency towards emotional distress characterized by high scores on social inhibition and negative affectivity traits, and CVD events and mortality), Kupper et al. found that selection of endpoint as well as age at baseline changed the results [41].

Our study has several strengths and limitations. A broad range of the Bortner Scale was observed in our study, and participants were followed for up to 37 years with low loss to follow-up. In the analysis, we took the subscales competitiveness and speed into account. We showed that these subscales were associated with mortality; whereas the total Bortner Scale was not. Furthermore, we showed that the results stayed significant after adjustment for lifestyle factors, including blood pressure as a clinical factor. Data on further potential adjustment variables like diabetes and prior coronary artery disease was not available. We nevertheless believe that these diseases are partially captured by measured blood pressure. High blood pressure is strongly related with cardiometabolic disorders. The health status of the participants in our study was in terms of mortality better than in the general population. Reasons for that may be health-interested participants' bias and the fact that all participants had to personally attend a clinical visit and thus to displace on their own. The Bortner Scale was developed to measure TABP, but it has already been discussed by others that it only comprises parts of TABP by measuring competitiveness and speed [17]. As no other instruments collecting information on TABP were available in our study, we investigated the association of competitiveness and speed with mortality, instead of specifically Type A behavior. Furthermore, we could not include other personality traits in the analysis. In fact, the shown association between CVD mortality and the competitiveness subscale in women might have been modified or confounded by hostility [35,42]. In the two study populations, the Bortner Scale was assessed very similarly. Nevertheless, pooling could have introduced bias, despite adjustment for study in all analyses. Moreover, one has to consider that we investigated the association with mortality and not with incident cases. Although having a long follow-up, the number of CVD-specific deaths in the strata was small and therefore the results have to be interpreted with caution. Finally, we cannot exclude that some associations were due to multiple testing.

We assume that the results of our analysis tend to underestimate the real association between mortality and the Bortner Scale, because as mentioned before, we expect our study population to be healthier than the general population [43].

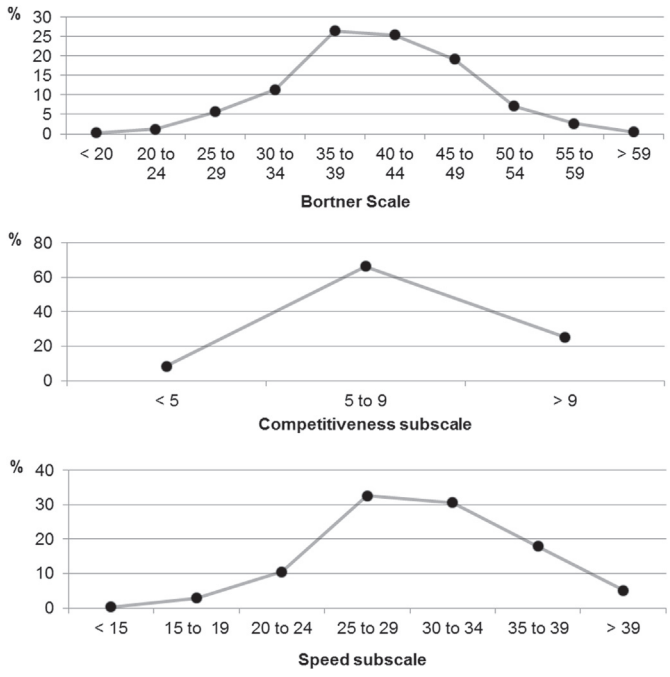

Fig. 1. Distribution of the Bortner Scale (n = 9922, 0 to 65), speed subscale (n = 10295, 0 to 15), competitiveness subscale (n = 10275, 0 to 45), men and women combined.

4.1. Conclusions

By considering the subscales competitiveness and speed of the Bortner Scale, we showed their sex-specific association with all-cause and CVD mortality. Future studies should also use this analytic approach to take into account the different dimensions of the Bortner Scale and stratify by sex to allow for replication of the results. The subscales of the Bortner Scale may be associated with CVD in an opposite manner. Competitiveness may increase the risk particularly in women, whereas speed could be neutral or even protective in men. Possibly, persons having the trait of competitiveness should be considered as population with increased CVD risk and be accordingly screened, counselled and treated.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial support

The present study was supported by the Swiss Cancer Research foundation (grant number KFS-3048-08-2012).

Author contributions

TL and DF led the conceptualization and research methodology, TL wrote the first draft of the manuscript, and conducted the statistical analysis. All authors critically appraised the submitted manuscript.

Acknowledgements

We thank the Swiss Federal Statistical Office for providing mortality and census data and for the support, which made the Swiss National Cohort and this study possible. The members of the Swiss National Cohort Study Group are Matthias Egger (Chairman of the Executive Board), Adrian Spoerri and Marcel Zwahlen (all Bern), Milo Puhan (Chairman of the Scientific Board), Matthias Bopp (both Zurich), Nino Künzli (Basel), Fred Paccaud (Lausanne) and Michel Oris (Geneva).

References

[1] M. Friedman, R. Rosenman, Type A Behavior and Your Heart, Alfred A. Knopf, New York, 1974.
[2] S.G. Haynes, M. Feinleib, E.D. Eaker, Type A behavior and the ten year incidence of coronary heart disease in the Framingham Heart Study, Act. Nerv. Super. (Praha) (1982) 57–77. Suppl 3(Pt 1).
[3] R.H. Rosenman, M. Friedman, R. Straus, C.D. Jenkins, S.J. Zyzanski, et al., Coronary heart disease in the Western Collaborative Group Study. A follow-up experience of 4 and one-half years, J. Chronic Dis. 23 (3) (1970) 173–190.
[4] C.D. Jenkins, R.H. Rosenman, S.J. Zyzanski, Prediction of clinical coronary heart disease by a test for the coronary-prone behavior pattern, N. Engl. J. Med. 290 (23) (1974) 1271–1275.
[5] R.H. Rosenman, R.J. Brand, R.I. Sholtz, M. Friedman, Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study, Am. J. Cardiol. 37 (6) (1976) 903–910.
[6] S.G. Haynes, M. Feinleib, W.B. Kannel, The relationship of psychosocial factors to coronary heart disease in the framingham study, Am. J. Epidemiol. 111 (1) (1980) 37–58.
[7] M. Friedman, C.E. Thoresen, J.J. Gill, D. Ulmer, L. Thompson, et al., Feasibility of altering type A behavior pattern after myocardial infarction. Recurrent Coronary Prevention Project Study: methods, baseline results and preliminary findings, Circulation 66 (1) (1982) 83–92.
[8] E.V. Nunes, K.A. Frank, D.S. Kornfeld, Psychologic treatment for the type A behavior pattern and for coronary heart disease: a meta-analysis of the literature, Psychosom. Med. 49 (2) (1987) 159–173.
[9] I. Shoham-Yakubovich, D.R. Ragland, R.J. Brand, S.L. Syme, Type A behavior pattern and health status after 22 years of follow-up in the Western Collaborative Group Study, Am. J. Epidemiol. 128 (3) (1988) 579–588.
[10] R.B. Shekelle, S.B. Hulley, J.D. Neaton, J.H. Billings, N.O. Borhani, et al., The MRFIT behavoir pattern study, II. Type A behavior and incidence of coronary heart disease, Am. J. Epidemiol. 122 (4) (1985) 559–570.
[11] M. Myrtek, Meta-analyses of prospective studies on coronary heart disease, type A personality, and hostility, Int. J. Cardiol. 79 (2) (2001) 245–251.
[12] M. Jokela, L. Pulkki-Råback, M. Elovainio, M. Kivimäki, Personality traits as risk factors for stroke and coronary heart disease mortality: pooled analysis of three cohort studies, J. Behav. Med. 37 (5) (2013) 881–889.
[13] H. Nabi, M. Kivimèki, M. Zins, M. Elovainio, S.M. Consoli, et al., Does personality predict mortality: results from the GAZEL French prospective cohort study, Int. J. Epidemiol. 37 (2) (2008) 386–396.
[14] K. Šmigelskas, N. Žemaitienė, J. Julkunen, J. Kauhanen, Type A behavior pattern is not a predictor of premature mortality, Int. J. Behav. Med. 22 (2) (2015) 161–169.
[15] C. Lemogne, S.M. Consoli, B. Geoffroy-Perez, M. Coeuret-Pellicer, H. Nabi, et al., Personality and the risk of cancer: a 16-year follow-up study of the GAZEL cohort, Psychosom. Med. 75 (3) (2013) 262–271.
[16] M. Jokela, G.D. Batty, T. Hintsa, M. Elovainio, C. Hakulinen, et al., Is personality associated with cancer incidence and mortality? An individual-participant meta-analysis of 2156 incident cancer cases among 42,843 men and women, Br. J. Cancer 110 (7) (2014) 1820–1824.
[17] J.R. Edwards, A.J. Baglioni, C.L. Cooper, The psychometric properties of the bortner type a scale, Br. J. Psychol. 81 (1990) 315–333.
[18] S. Böthig, WHO MONICA Project: objectives and design, Int. J. Epidemiol. 18 (3) (1989) 29–37.
[19] F. Gutzwiller, B. Nater, J. Martin, Community-based primary prevention of cardiovascular disease in Switzerland: methods and results of the National Research Program (NRP 1A), Prev. Med. 14 (4) (1985) 482–491.
[20] M. Bopp, A. Spoerri, M. Zwahlen, F. Gutzwiller, F. Paccaud, et al., Cohort profile: the Swiss national cohort—a longitudinal study of 6.8 million people, Int. J. Epidemiol. 38 (2) (2009) 379–384.
[21] M. Bopp, J. Braun, D. Faeh, F. Gutzwiller, Establishing a follow-up of the Swiss MONICA participants (1984-1993): record linkage with census and mortality data, BMC Public Health 10 (2010) 562.
[22] M. Bopp, J. Braun, F. Gutzwiller, D. Faeh, Health risk or resource? Gradual and independent association between self-rated health and mortality persists over 30 years, PLoS One 7 (2) (2012) e30795.
[23] D. Faeh, P. Marques-Vidal, A. Chiolero, M. Bopp, Obesity in Switzerland: do estimates depend on how body mass index has been assessed? Swiss Med. Wkly. 138 (2008) 204–210.
[24] National Institutes of Health, Clinical guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults - the Evidence Report. No. 98-4083, 1998.
[25] H. Nabi, M. Kivimäki, M.G. Marmot, J. Ferrie, M. Zins, et al., Does personality explain social inequalities in mortality? The French GAZEL cohort study, Int. J. Epidemiol. 37 (3) (2008) 591–602.
[26] D.W. Johnston, D.G. Cook, A.G. Shaper, Type A behaviour and ischaemic heart disease in middle aged British men, Br. Med. J. Clin. Res. Ed. 295 (6590) (1987) 86–89.
[27] I. Kawachi, D. Sparrow, L.D. Kubzansky, A. Spiro, P.S. Vokonas, et al., Prospective study of a self-report type a scale and risk of coronary heart disease, Circulation 98 (5) (1998) 405–412.
[28] A. Ikeda, H. Iso, I. Kawachi, M. Inoue, S. Tsugane, JPHC Study Group. Type A behaviour and risk of coronary heart disease: the JPHC Study, Int. J. Epidemiol. 37 (6) (2008) 1395–1405.
[29] A.H. Mann, P.J. Brennan, Type A behaviour score and the incidence of cardiovascular disease: a failure to replicate the claimed associations, J. Psychosom. Res. 31 (6) (1987) 685–692.
[30] J.E.J. Gallacher, P.M. Sweetnam, J.W.G. Yarnell, P.C. Elwood, S.A. Stansfeld, Is type A behavior really a trigger for coronary heart disease events? Psychosom. Med. 65 (3) (2003) 339–346.
[31] M. Jokela, G.D. Batty, S.T. Nyberg, M. Virtanen, H. Nabi, et al., Personality and all-cause mortality: individual-participant meta-analysis of 3,947 deaths in 76,150 adults, Am. J. Epidemiol. 178 (5) (2013) 667–675.
[32] M. André, E. Billstedt, C. Bengtsson, T. Hällström, L. Lissner, et al., Personality in women and associations with mortality: a 40-year follow-up in the population study of women in Gothenburg, BMC Womens Health 14 (2014) 61.
[33] G.D. Batty, M. Jokela, M. Kivimaki, M. Shipley, Examining the long-term association of personality with cause-specific mortality in London: four decades of mortality surveillance in the original whitehall smoking cessation trial, Am. J. Epidemiol. 184 (6) (2016) 436–441.
[34] B.A. Shipley, A. Weiss, G. Der, M.D. Taylor, I.J. Deary, Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: a 21-year prospective cohort study, Psychosom. Med. 69 (9) (2007) 923–931.
[35] Y. Chida, A. Steptoe, The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence, J. Am. Coll. Cardiol. 53 (11) (2009) 936–946.
[36] Nakaya N, Tsubono Y, Hosokawa T, Hozawa A, Kuriyama S, et al. Personality and mortality from ischemic heart disease and stroke. Clin. Exp. Hypertens. 27(2–3):297–305.
[37] A.I. Lazzarino, M. Hamer, E. Stamatakis, A. Steptoe, Low socioeconomic status and psychological distress as synergistic predictors of mortality from stroke and coronary heart disease, Psychosom. Med. 75 (3) (2013) 311–316.
[38] C. Lemogne, P. Meneton, E. Wiernik, A. Quesnot, S.M. Consoli, et al., When blue-collars feel blue: depression and low occupational grade as synergistic predictors of incident cardiac events in middle-aged working individuals, Circ. Cardiovasc Qual. Outcomes 10 (2) (2017).
[39] N. Nakaya, Y. Tsubono, T. Hosokawa, Y. Nishino, T. Ohkubo, et al., Personality and the risk of cancer, J. Natl. Cancer Inst. 95 (11) (2003) 799–805.
[40] C. Lemogne, S.M. Consoli, H. Panjo, H. Nabi, M. Goldberg, et al., Personality and hormone therapy use among postmenopausal women in the GAZEL cohort study, Fertil. Steril. 98 (4) (2012) 929–936.
[41] N. Kupper, J. Denollet, Explaining heterogeneity in the predictive value of Type D personality for cardiac events and mortality, Int. J. Cardiol. 224 (2016) 119–124.
[42] W.J. Kop, D.S. Kranitz, Type A behaviour, hostility and coronary artery disease, in: A. Baum, S. Newman, J. Weinman, R. West, C. McManus (Eds.), Cambridge handbook of Psychology, Health, and Medicine, Cambridge University Press, Cambridge, 1997, pp. 183–186.
[43] T. Lohse, D. Faeh, M. Bopp, S. Rohrmann, Swiss national cohort study group. Adherence to the cancer prevention recommendations of the World cancer research fund/American Institute for cancer research and mortality: a census-linked cohort, Am J Clin Nutr. Am. Soc. Nutr. 104 (3) (2016) 678–685.